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A Journal of Neurology

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CONTENTS.

	PAGE
Changes in the Nervous System in Acute Porphyria. D. Denny-Brown and Daniel Sciarra	1
The E.E.G. in the Prognosis of War Neurosis. M. E. Heppenstall, Denis Hill and Eliot Slater	17
The Arterial Relations of the Internal Auditory Meatus. Sydney Sunderland	23
Vascular Diseases of the Nervous System. Charles D. Aring	28
Traumatic Injuries of Peripheral Nerves. Sydney Sunderland	56
Transient Disturbances following Gunshot Wounds of the Head. W. Ritchie Russell	79
A Study of Pupillary Inequalities in Man. Eric A. Turner	98
The Adipose Tissue of Peripheral Nerves. S. Sunderland	118
Abnormal Suppression of Cortical Frequencies. Denis Williams and Joan Reynell	123
Spinal Tracts subserving Micturition in a Case of Erb's Spinal Paralysis. J. McMichael	162
The "Discharging Lesion" in Neurology. J. Purdon Martin	167
A Case of Topographical Disorientation associated with a Unilateral Cerebral Lesion. Andrew Paterson and O. L. Zangwill	188
Folie à Deux in Uniovular Twins Reared Apart. W. H. Craike and Eliot Slater, with the assistance of G. Burden	213
The Development of the Human Lateral Geniculate Body. E. R. A. Cooper	222
The Intraneural Topography of the Radial, Median and Ulnar Nerves. Sydney Sunderland	243
The Role of Galvanism in the Treatment of Denervated Voluntary Muscle in Man. Shirley Jackson	300
The Interrelation of the Strio-pallidum and the Thalamus in the Macaque Monkey. P. Glees	331
Note on the Lateral Geniculate Body. W. E. Le Gros Clark	347
Notices of Recent Publications	73, 165, 240, 350

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ERRATA.

"THE ELECTRICAL DIAGNOSIS OF PERIPHERAL NERVE INJURY."

Ritchie, A. E., *Brain*, vol. 67, part 4, pages 314-330, 1944.

The following legends applicable to the text figures have been omitted in error, and should be read in place of those now given in that paper.

FIG. 1.—The variation of rheobase with electrode displacement from the "motor point" of normal muscle. Mean result of 25 measurements on various forearm muscles. Inset: type of stimulating electrode used.

FIG. 2.—The variation of the Voltage-Time curves in the same muscle of a normal subject. Range figured represents the mean, plus and minus the Standard Deviation, of a series of 100 measurements carried out over a period of three months. Muscle—left first dorsal interosseous of hand.

FIG. 3.—Composite graph of the Voltage-Time curves of normal and denervated muscle. Denervated figures from 27 cases of known surgical denervation; normals from 50 unselected cases. Each range represents mean plus and minus Standard Deviation. Assorted hand and forearm muscles grouped together.

FIG. 4.—Case C. F. Complete division of radial nerve above elbow. Denervated extensor digitorum communis muscle A, on admission; B, after two weeks' physiotherapy; C, after operation. N = control records from contralateral normal muscle.

FIG. 5.—Case G. S. Paresis of ulnar nerve from occupational pressure. Spontaneous recovery. Voluntary movement never entirely lost. Flexor carpi ulnaris muscle; N = normal contralateral.

FIG. 6.—Case W. J. M. Functional paralysis. Reappearance of radial paralysis in nerve known to have been injured four years previously, and to have recovered. Ext. dig. communis muscle; N = normal contralateral.

FIG. 7.—Case W. H. P. Complete radial nerve section and recovery after suture. A = on admission; 8 = eight weeks after operation. First sign of re-innervation appears at ten weeks; voluntary movement at sixteen weeks. Ext. dig. communis muscle; N = normal contralateral.

FIG. 8.—Case M. Y. H. Radial nerve injury with fracture of humerus. A = on admission. First sign of re-innervation twenty-five weeks after nerve suture; voluntary power detectable at thirty-four weeks. Ext. dig. communis muscle; N = normal contralateral.

FIG. 9.—Case W. T. A. Facial nerve section and spontaneous recovery. Gradual recovery of excitability and muscle tone without individual muscle movement. Occ.-frontalis muscle on forehead; N = normal contralateral.

FIG. 10.—The Voltage-Current relationship of a rectangular stimulus applied (A) to a trough of saline and (B) to the forearm muscles with the usual electrodes in each case. Recorded with double-beam oscillograph: V = applied voltage at electrodes, C = resultant current flow in tissues. Length of stimulus 10 milliseconds.

MARCH, 1945

BRAIN

VOL. 68, PART 1.

CHANGES IN THE NERVOUS SYSTEM IN ACUTE PORPHYRIA

BY D. DENNY-BROWN AND DANIEL SCIARRA.[1]

THE nervous complications of acute porphyria were first described by Ranking and Pardington in 1890, and by 1911 Günther was able to collect 14 recorded cases for his excellent paper. The relationship between porphyria and the clinical syndrome has been reviewed at length by Mason, Courville, and Ziskind (1933) and Waldenström (1937) who also report further cases. The neuritic symptoms may occur in relation to spontaneous attacks of porphyria (hæmatoporphyria acuta idiopathica) or when some known toxic agent such as sulphonal or trional has precipitated the attack (hæmatoporphyria acuta toxica). Indeed these two varieties differ only in the relationship to the drug in the second, and there is good evidence that in both there is an underlying metabolic defect allied to the fault which determines hæmatoporphyrinuria congenita.

The excreted pigments, present in small amounts in normal urine, are classed as porphyrins Type I (including the photoporphyrins), and Type III (including uroporphyrin and coproporphyrin) (Waldenström, 1937; Dobriner and Rhoads, 1940). Increased amounts of coproporphyrin are excreted ("porphyrinuria") in many conditions, notably in liver disease. The excretion of large amounts of photoporphyrins occurs in congenital porphyria. The pigment excreted in acute idiopathic or toxic porphyria is apparently chiefly uroporphyrin, and the darkening of the urine on exposure to light due to a related Type III leucoporphyrin (Dobriner and Rhoads).

The condition of acute idiopathic porphyria discussed in this paper is more common in females and is often inherited as a Mendelian dominant (Waldenström). An instance has been reported of first attack at the age of 3 years (Rothman, 1926) but most usually the first manifestation is in the third or fourth decade. The attack begins usually with

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acute abdominal symptoms—colicky pains with nausea, vomiting and constipation, with leucocytosis, associated usually with the well-known burgundy-coloured pigmentation of the urine on exposure to light. At the height of the illness toxic delirium, or an acute ascending neuritis of Landry type, or both, may arise. Convulsions may occur in the delirious stage. There may be complete recovery from the attack, but the neuritis tends to bulbar manifestations in a severe attack and these are the usual cause of fatal termination. Minor bouts characterized by vague gastro-intestinal symptoms have often preceded severe or fatal attacks. The onset of nervous symptoms commonly occurs as the abdominal pains and porphyrinuria lessen, and may progress rapidly to dysphonia and dysphagia in a few days, or rarely in a much slower course over some weeks. The paralysis is always flaccid, with loss of tendon reflexes, and sensory loss is seldom demonstrable, though pain is prominent and paræsthesiæ are complained of. The mortality from peripheral neuritis is estimated to be over 50 per cent. in the first attack by Mason *et al.* (1933).

The pathological findings, apart from the central nervous system, have been limited to pigmentation of the skin and quantities of both iron-free and iron-containing pigment in the liver. Degeneration of myelin sheaths and axis cylinders, particularly in the nerves of the lower extremities, has been described in a number of cases. Loeffler (1919), however, found only hyperæmia of the nerves in spite of extensive paralysis, and Rothman (1926) and Borst and Königsdorffer (1929) found no changes in the nerves in their cases. Mason *et al.* conclude that the patchy and selective nature of the motor paralysis is unexplained. In their own 2 cases infiltration of the peripheral nerves with round cells also occurred. Baker and Watson (1945) noted severe degeneration in the nerves of the lower limbs in their case, but in the upper limbs the affection of the nerves followed the more usual patchy character, with "early demyelination." The axis cylinders in such patches were swollen and stained poorly but maintained continuity. In more severe lesions in the lower limbs degeneration was more advanced in the centre of each bundle. The vessels were congested and there was occasional perivascular exudation.

Changes in the nerve cells of the dorsal root ganglia in the nature of acute swelling, pigmentation and degenerative fragmentation have been described by Courcoux *et al.* (1929), Bostroem (1920) and Mason *et al.* (1933). Bostroem also described proliferation of capsular cells. Mason *et al.* describe similar changes in the nerve cells of sympathetic ganglia, to which they attribute the abdominal symptoms. Several

writers (Bostroem, Courcoux *et al.*, Mason *et al.*) describe changes in the ganglion cells of both dorsal and ventral horns in the spinal cord, usually more evident in anterior horn cells. These changes have taken the form of chromatolysis with accumulation of lipoid pigment sufficient to dislocate the cytoplasm and nucleus to one side of the cell, and cytoplasmic or nuclear vacuolation. Mason *et al.* described the collection of cytoplasmic pigment granules near the nuclear membrane in some cells. Changes in cortical ganglion cells if present at all are few and confined to mild chromatolysis and shrinkage. Acute swelling of the oligodendroglia is common. Severe chromatolytic changes in the Purkinje cells of the cerebellum were also found by these investigators. Eichler (1932) found œdema of the brain. Baker and Watson (1945) found foci of swelling and vacuolation of myelin in the white matter of both hemispheres in small circumscribed areas, without damage to axis cylinders. There was also a mild diffuse astrocytic proliferation. Courcoux *et al.* found some marginal demyelination of the anterolateral tracts of the lumbar spinal cord. Such central demyelination has not been found by others.

We have recently encountered the two cases of acute "idiopathic" porphyria which are reported here. The first is cited as an example of the manifestation in the form of an acute and very transient "toxic delirium," the second in the more usual form of delayed neuritis with recovery and a second fatal attack two years later. In this case the pathological findings offer an explanation for some of the clinical features of the disease.

Case 1.—E. D., aged 46, an unmarried electric cableman, was admitted to the Boston City Hospital in a delirious state on November 14, 1944. He had been perfectly well until six days before admission when he came home from work complaining of generalized moderately severe pain in the chest radiating to both shoulders and across the back, and associated with moderate dyspnœa. There was no cough, fever, or chill. The next day he returned to work, though some feeling of tightness persisted, but returned home in the afternoon because of increase in the discomfort and a feeling of weakness. The sensation again disappeared after a night's rest, but on the third day the fingers and hands were found to be shaky. He had difficulty in grasping objects in either hand, and felt very nervous. In the next three days he became gradually more tremulous and developed some fever. The evening before admission he became confused and delirious, and was referred to the hospital with a diagnosis of delirium tremens.

Family history.—Three brothers all died in middle or late middle age of unknown causes. No history of dark urine or of symptoms clearly referable to porphyria in the family was obtained except that the patient thinks both of his parents "passed dark urine." There was no means of confirming this suspicion.

Personal history.—The diet had been adequate. He was accustomed to take three to four glasses of beer a day and about 1½ oz. of whisky. His relatives denied

inebriation and declared that he spent his evenings at home. He occasionally took aspirin, and had been given phenobarbital by his own doctor in the early stage of the illness. He denied any previous illness, and his only hospital admission had been for a fractured ankle in 1942.

Examination.—On admission his temperature was 100·0°, pulse 80, respiration 25, blood-pressure 140/85 mm.Hg. He was disoriented in place, time, and person, and kept up a conversation with an imaginary friend "Frank." He glanced suddenly to one or other side at intervals, as if having visual hallucinations. He later stated that he kept hearing people talking to him and that there were bird-like animals on the wall. These latter disappeared if he closed his eyes. He responded to questions with completely irrelevant statements. He appeared well developed and well nourished. There was a slow side-to-side tremor of his head and irregular, rapid tremors of the hands, tongue, and lower limbs, increased by any attempted voluntary movement. There was a fine, light punctate rash covering the chest and abdomen and around the knees, ankles, and hands. The pupils were dilated and reacted well to light and accommodation. The only defect in the cranial nerve function was the tremor of the tongue. Movements of the upper limbs were jerky and poorly co-ordinated. The tendon-jerks were all hyperactive and the plantar responses both flexor. There was no neck rigidity. He was incontinent of urine.

Course.—On the day following admission the temperature rose to 101·4° (rectal), and white count to 14,000 per c.mm. The delirium was controlled by paraldehyde. Both the delirium and tremor steadily lessened during the first two days. The tremor became finer and involved only the lips, tongue and hands. By the third day he was oriented in all spheres and responded sensibly to questions. The rash and tremor also disappeared by this day. The first urine specimen was obtained on the third day and was a dark red-brown colour, which after examination of an ether extract under ultra-violet light was reported to contain porphyrins.

On questioning the patient now stated that he had passed dark-coloured urine every second or third morning for about two years, and that two weeks before admission the colour became darker than usual and remained constantly so.

On the fourth day after admission the temperature and white count were normal and all symptoms had disappeared. The urine was still red-brown, but on the fifth day the colour was the usual amber, and so remained up to the date of discharge from the hospital on the eighth day. The porphyrins, however, still remained present in varying concentration as follows: 3rd hospital day four plus by ultra-violet fluorescence. 4th day four plus, 5th day one plus, 6th day three plus, 7th day three plus, 8th day two plus, 16th day (follow-up) two plus.

Other laboratory data.—The urine varied from 1016 to 1020 in S.G., and only once had a slight trace of albumin. There was no sugar, bile, or abnormal cellular content.

Blood-count: Hæmoglobin 100 per cent., W.B.C. 6,600 with normal differential count on November 14, 14,150 on November 15, 6,500 on November 17. Blood Hinton test negative. N.P.N. on November 14, was 52 mgm. per 100 cc., on November 17, 42 mgm. Stools negative to guaiac test. Urine urobilinogen present only up to 1:64 dilution. Radiograms of the chest were negative. E.K.G. within normal limits.

Comment.—The clinical state of this patient paralleled that of the condition of delirium tremens. In view of his admission of consumption of alcohol the possibility that the condition was in fact an exceedingly

brief and benign attack of delirium tremens cannot be eliminated. The coincidence of the disorder with a bout of severe porphyrinuria, and the prominence of a "toxic" delirium in our second case, and other cases of a similar type, raise questions to which we will return in our discussion. The method of estimations of porphyrins, which was kindly done for us by Dr. Janet Watson of the Thorndike Laboratory, was a modification of the method of Brugsch and Keys (1938), as used by Kark and Meiklejohn (1941). Watson's test for uroporphyrin was also positive.

Case 2.—E. T., a white male, aged 32, a welder by occupation. Apart from measles and chicken-pox in childhood there was no history of any illness of note before 1942, and no knowledge of family liability to similar disorder. He first complained of pains and cramps in the upper abdomen on December 6, 1942. After five days he was admitted to a hospital for investigation.

Through the kindness of Dr. Maxwell Macdonald we ascertained that at that time the only clinical abnormality to be found on examination was tenderness over the whole abdomen with moderate resistance to palpation. The blood-pressure was 110/60 mm. The pain was sufficiently severe to require morphia and continued until January 2, 1943. In this period there was severe constipation but gastro-intestinal investigation by barium meal revealed no filling defect in stomach or duodenum and a normal passage of a barium meal to the colon which was markedly distended with gas. The gall-bladder was normal in opaque dye test. On December 18, the patient had a severe generalized convulsion, another on 19th and three more during the night of December 20. These were treated with barbiturates. On January 2 the abdominal pain was gradually subsiding and had gone by January 5, on which date he began to complain of pains and some weakness in both arms. There was no affection of the lower limbs at that time but by January 9 there was great flaccid weakness in all movements of both upper limbs. By January 11, both lower limbs had become weak, and nine days later the trunk musculature was also involved. With hot fomentations the pain in all limbs was somewhat relieved and some improvement in muscular power was first noted on January 26. He was able to walk again three days later though the weakness in the arms was sufficient to prevent his feeding himself until discharged from hospital greatly improved on February 6. There had been no further convulsions.

Laboratory data during the hospital admission showed a consistently amber-coloured urine of S.G. 1·019 to 1·027, with many hyaline casts and 3 to 5 R.B.C. in the first week of admission; thereafter entirely normal. Blood studies: On 11.12.42 R.B.C. 4,320,000, hæmoglobin 64·5, W.B.C. 11,150, polys. 71 per cent., lymph. 23 per cent., mono. 5 per cent., eosinophils 1 per cent. On 14.12.42 W.B.C. 12,850, on 18.12.42 W.B.C. 18,100, polys. 82 per cent., lymph. 11 per cent., mono. 6 per cent., eosin. 1 per cent. N.P.N. 21.12.42 72 mg., 23.12.42 55·5 mg., 2.1.43 44 mg. per 100 c.c. Blood sugar 18.12.43 131 mg. C.S.F. 1 cell, 0 R.B.C., glob. neg., total protein 27 mg., sugar 93 mg.

The patient made a gradual but complete recovery in the following few months and returned to his employment without further difficulty for the next two years.

On March 10, 1944, he had had a sore throat for one day when abdominal pain and cramps again commenced. Of possible significance in relation to the transient sore throat is the fact that his three children developed scarlet fever one week after the onset of the patient's illness. On March 13 the abdominal

cramps caused his readmission to hospital for three days. The abdomen offered resistance to palpation. The pains were greater at the costo-vertebral angles and continued as on his first admission for three weeks, then subsiding gradually. In the first ten days the urinary output was greatly diminished, but amber in colour, S.G. 1·005 to 1·025, containing no albumin, no sugar and an occasional W.B.C. with rare hyaline cast. Blood-count 3,340,000 R.B.C., hæmoglobin 73·8, 13,500 W.B.C., polys. 82 per cent., lymph. 18 per cent. Blood Hinton test negative, N.P.N. 40 mg., 38·5 mg. per 100 c.c. on 24.3.44. Blood sugar 83 mg. per 100 c.c.

On March 23 the patient was drowsy and in the following twenty-four hours five generalized convulsions were recorded. Following the administration of barbiturates no further convulsions occurred, but the patient remained drowsy. In the following days the gradual onset of weakness of both upper limbs was found. By April 1, weakness had spread to both lower limbs and the trunk musculature, and speech was slurred. On April 4 he was unable to speak coherently or to swallow. The spinal fluid on March 25 was clear, with 2 cells per cm., and negative to Pandy's test.

On April 4, the patient was transferred to the Neurological Service, Boston City Hospital. On admission he was found to be confused and disoriented in time and place. The skin was pale without evidence of eruption. His speech was very dysarthric and the palate failed to move in phonation. He could co-operate in simple clinical examination. The corneal reflexes were absent bilaterally, and there was almost complete paralysis of the facial musculature on both sides. The trapezius and sterno-cleido-mastoids were weak. The tongue could be protruded only slightly. There was complete loss of motor power in all four limbs and trunk except for slight flexion and extension of the fingers and toes, and laboured respiration with the accessory musculature.

The tendon reflexes and superficial reflexes were all absent. There was a good response to touch and pin-prick in all parts, but vibratory sense was diminished at the wrists and ankles. Position sense was seldom reported accurately (? impaired co-operation).

The patient was kept in a mechanical respirator for three days without obvious change, but on the fourth day he became more confused and irrational, very cyanotic and later comatose, in which state he died on April 7, four weeks from the onset of the final attack.

Laboratory studies in the last three days showed a hæmoglobin of 67 per cent., 14,400 W.B.C., N.P.N. 44 mg. per 100 cc. Heterophile agglutination was negative, Widal negative, Hinton negative. Nose and throat culture negative for Klebs-Loeffler bacillus. Spinal fluid obtained post mortem showed no cells, total protein content 33 mg. per 100 c.c., negative Pandy, negative colloidal gold.

During the last four days the urine was noted to vary in colour from a deep orange to burgundy red. It was acid in reaction, S.G. 1·020-1·021, with a very slight trace of albumin, occasional casts, and red and white blood cells. Porphyrin was present in both the aldehyde and ether extract—HCl concentrate tests.

Pathological diagnosis.—(1) Congestion and œdema of the lungs with early lobar pneumonia of right upper and lower lobes.

(2) Findings consistent with porphyrinuria.

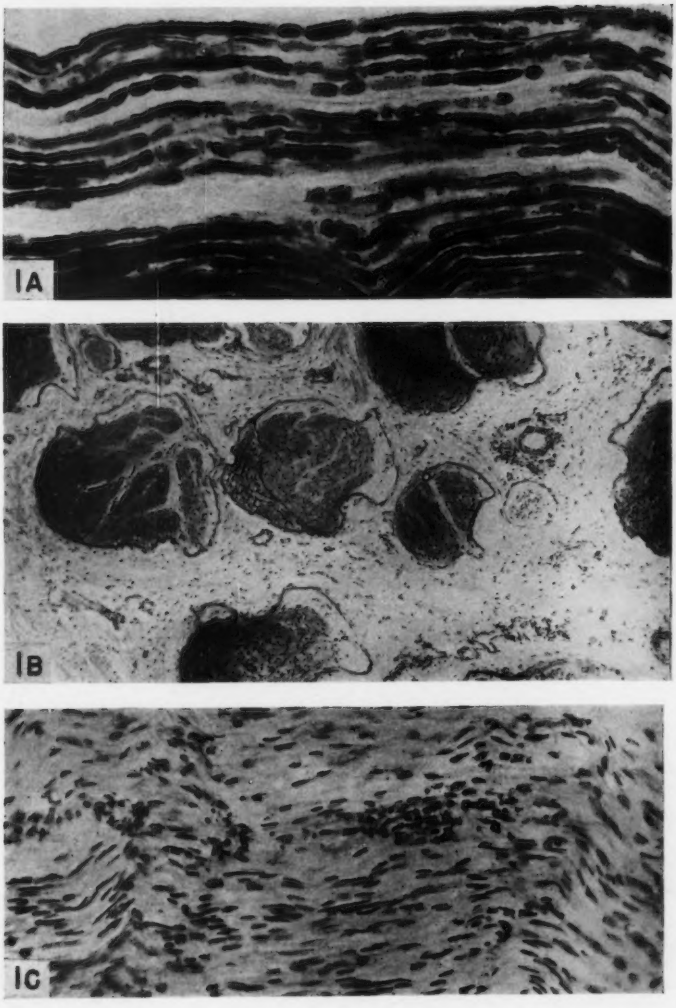
(3) Polyneuritis, with ganglion cell changes and patchy demyelination of the central nervous system.

(4) Mild chronic cholecystitis.

(5) Chronic passive congestion of the liver with pigmentation.

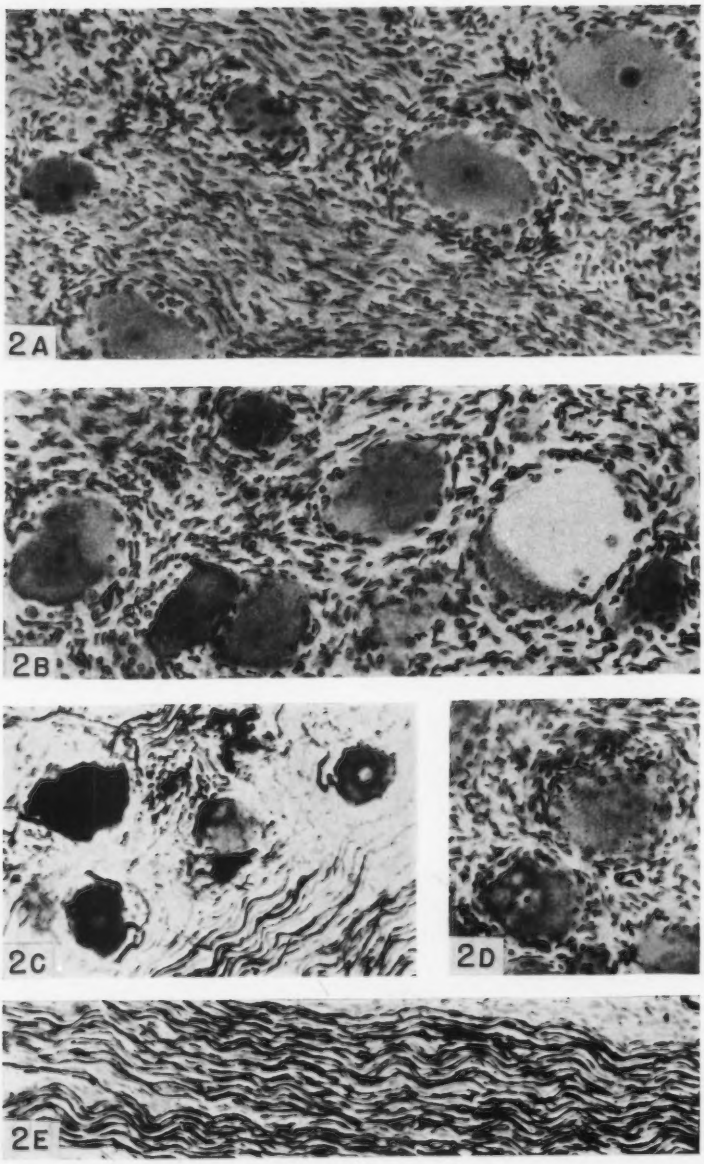
(6) Terminal patchy tubular necrosis of the kidneys.

PLATE I.



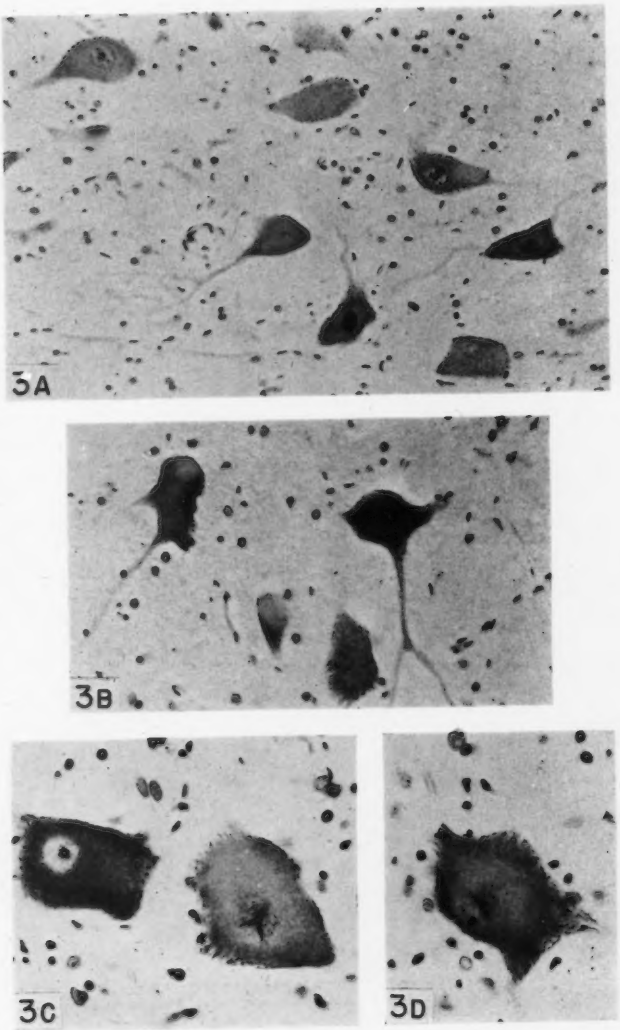
To illustrate article by D. Denny-Brown and Daniel Sciarra.

PLATE II.



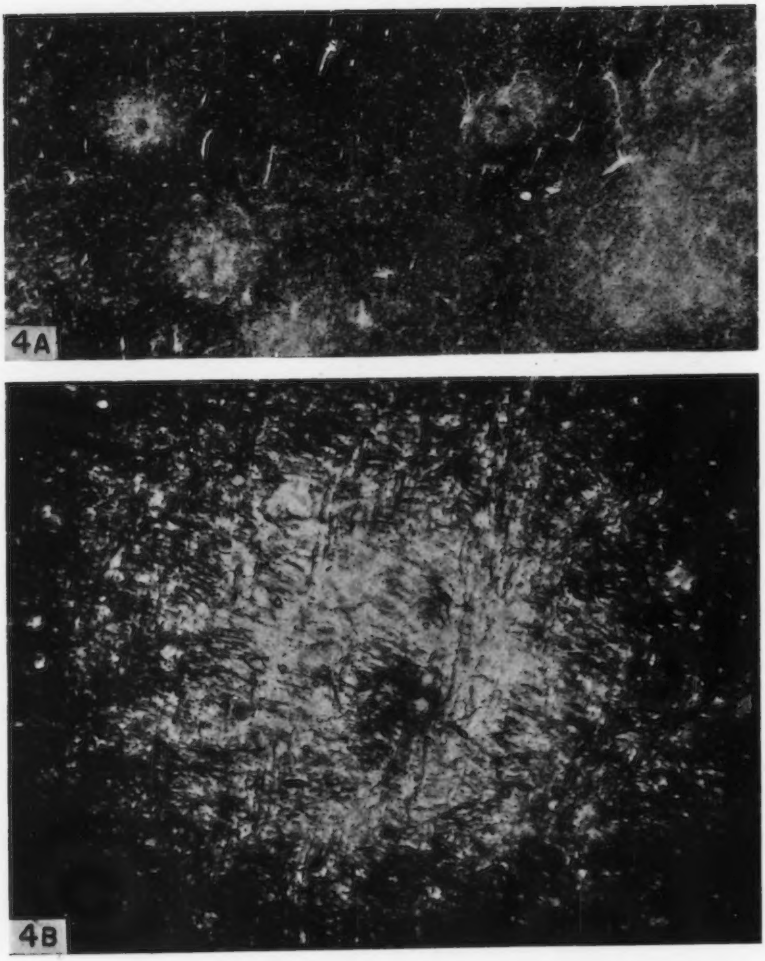
To illustrate article by D. Denny-Brown and Daniel Sciarra.

PLATE III.



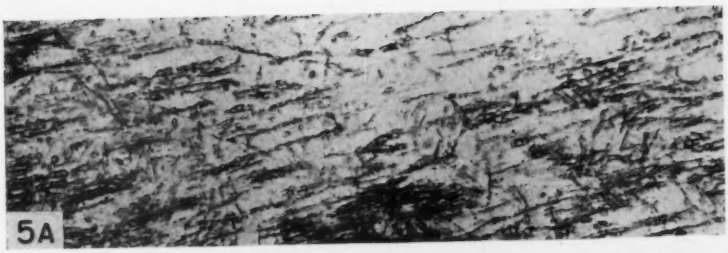
To illustrate article by D. Denny-Brown and Daniel Sciarra.

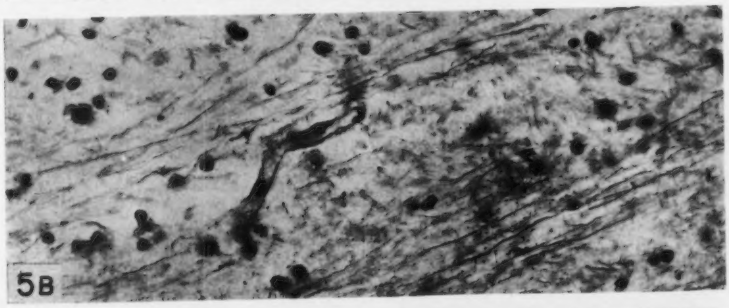
PLATE IV.

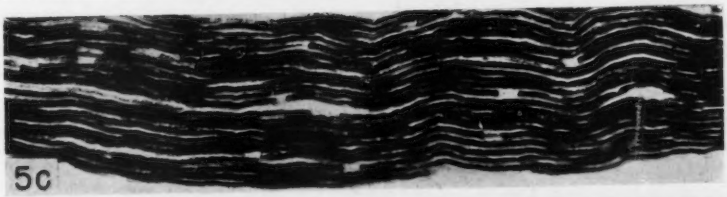


To illustrate article by D. Denny-Brown and Daniel Sciarra.

PLATE V.







To illustrate article by D. Denny-Brown and Daniel Sciarra.

Post mortem findings.—Autopsy was carried out eighteen hours post mortem. Body length 170 cm. Body-weight 160 lb.

The body was that of a moderately thin, well-developed, white male without external abnormality. The surfaces of the peritoneal cavity were smooth and shining, and the abdominal organs were in natural relationship. The liver extended 2 cm. below the xiphoid and was at the right costal margin in the mid-clavicular line. Both pleural cavities were dry, with smooth surfaces. There was 20 c.c. of clear yellow fluid in the pericardial cavity. The heart was in the usual position, and no abnormalities of the valves were discovered. The coronary arteries showed minimal atherosclerosis throughout, with no calcification or occlusion. The myocardium was of natural colour and showed only two very small areas of fibrosis near the apex of the interventricular septum. There was no infarction.

The lungs were subcrepitant throughout. On section they exuded a rather thick, red-purple fluid with an opalescent cast. The bronchial mucosa was markedly injected and covered with mucous material.

The spleen weighed 160 grm., was of the usual size and shape and presented no abnormality on section.

Gastro-intestinal tract: The stomach was moderately dilated and filled with a brown thin liquid material. The entire bowel was negative. The contained fæces were green-brown. The mesenteric nodes were moderately enlarged, each being from 0·5 to 0·7 cm. in diameter. On section, their cut surface was grey-brown and they were soft and homogeneous.

The pancreas was of normal appearance. The liver weighed 1,400 grm. and presented a smooth surface. The cut surface was of the usual red-brown colour with an unusual purple tinge. There were small light grey areas (1 mm.) throughout and these appeared to be present between the lobules.

The gall-bladder was small but otherwise normal in appearance. It was only partly filled with a brown bile which could be forced from the gall-bladder into the duodenum. The kidneys were of natural size, shape, and weight. They stripped easily revealing a red, smooth surface. They were rather firm and cut with a somewhat fibrous feel. Their cut surface revealed the usual architecture, with normal pelves and ureters. The adrenals were present bilaterally and in good preservation as was also the thyroid gland.

The bladder and genitalia were normal.

The aorta was very mildly atherosclerotic in its abdominal portion.

The brain was sectioned after fixation. The external surface of the brain was quite normal in appearance and the leptomeninges were clear. The large cerebral and basilar arteries were thin walled. There were no gross lesions in the cerebrum or brain-stem, spinal cord or peripheral nerves.

The spinal cord, various lumbosacral dorsal root ganglia, and portions of the sciatic, posterior tibial, sural, external cutaneous, vagus, and phrenic nerves were of normal appearance, and were preserved in 10 per cent. formalin for microscopic examination.

Microscopic examination.—The epicardium, endocardium and myocardium were normal. The lungs showed congestion and œdema, and early lobar pneumonia of right upper and lower lobes.

The pulp of the spleen was extremely congested by red blood cells and the sinusoids lined by swollen endothelial cells and filled with red blood cells. There was a slightly increased number of polymorphonuclears in the pulp.

The sinusoids of the liver near the central veins were markedly widened with

narrowing of the hepatic cord. There was little congestion and no necrosis or polymorphonuclear infiltration. Many of the liver cells contained large, clear, round vacuoles, and most contained clumps of coarse granules, green to yellow-brown in colour, many giving a positive staining reaction for iron, others not.

Kidneys: There was no abnormality of any kind in the blood-vessels. There was a minimal amount of lymphocytic, plasma cell and polymorphonuclear infiltration throughout the cortex. A few tubules contained polymorphonuclears and a few colloid casts. In the cells of many of the collecting tubules there were irregular green granules of varying size. Very few granules gave a positive iron reaction. Some of the collecting tubules contained green amorphous casts. A few tubules showed recent necrosis and there was evidence of regeneration in others. Many of the glomeruli showed a slight fibrous thickening of the capsules and some swelling of the epithelial lining of Bowman's capsule, and a few were atrophic. There was mild subcapsular atrophy.

The pancreas was normal, and the adrenals and thyroid showed no essential changes. The mesenteric lymph nodes examined were of normal architecture. The gall-bladder showed the changes of a mild chronic cholecystitis.

Nervous system: Sections of peripheral nerves, spinal ganglia, spinal cord, medulla, cerebellum, mid-brain and cerebrum were available for examination.

Sections of the peripheral nerves embedded in celloidin were stained by cresyl violet, hæmatoxylin and phloxine, phosphotungstic acid hæmatoxylin, and Gros-Bielschowsky for axis cylinders. In addition frozen sections were stained for fat by Sudan III, and for myelin by Spielmeyer's method.

Sections of a piece of the proximal portion of the sciatic nerve showed patchy dilatation of the perineural spaces around some bundles with occasional lymphocytes and wandering histiocytes in the fluid present in this situation. Axis cylinder stains failed to show any degeneration of these structures, though many axons were irregular in calibre in the œdematous areas. The myelin sheaths showed no abnormality in Spielmeyer and Sudan sections. At other levels no change whatever could be found.

The posterior tibial nerve in one segment appeared entirely normal except for mild œdema of one fasciculus. In other pieces the myelin showed patches of beading and irregularity (fig. 1*a*) associated with œdema under the perineurium. Cell stains of such areas showed mild proliferation of Schwann cells and endoneurial fibroblasts (fig. 1*c*) with slight perivascular accumulation of mononuclears. This patchy disorder of myelin sheaths was accompanied by some thinning and irregularity of staining of the axis cylinders, but without interruption. The fibrillary sprouting of regenerating axis cylinders was also absent.

At one level nearly every fasciculus showed œdema with lifting of the perineurium, seen particularly clearly in transverse section (fig. 1*b*). This phenomenon was readily distinguishable from artefact by the presence of mononuclear histiocytes and fibroblasts in the exudate. The vessels, both in the epi- and endoneurium, appeared undamaged at any level. At the borders of an area of damaged myelin an occasional myelin sheath that was otherwise intact showed an isolated gap of about 0·1 mm. in length as in the lower part of fig. 1*a*. Except for small granules in a few histocytes there was no free fat in Sudan sections, and the characteristic ovoids and vacuolated histiocytes of Wallerian degeneration were absent. The myelin sheaths were resumed distal to each lesion.

Sections of a sural cutaneous nerve, phrenic nerve, and vagus nerve showed no degeneration in myelin or axis cylinders and no cellular reaction.

Sections of the 5th lumbar and 1st sacral dorsal root ganglia showed changes

in the ganglion cells. Many were greatly swollen with disappearance of the Nissl substance except at the extreme margin (fig. 2*a*), and a halo around the nucleus which had become diffusely eosinophilic. In some rare examples the cytoplasm appeared to be greatly displaced by a mass of unstaining subcapsular substance (? œdema) as in fig. 2*b*. Other cells had become shrunken with very dark eosinophilic nucleus and granular cytoplasm (fig. 2*a*). In these the granules stained with Sudan III and silver. The nuclear change appeared to be identical with that called "homogeneous nuclear shrinkage" by Marburg (1902). The normal lipoid at one pole of the cell was prominent but not increased in amount. In a few cells there was vacuolation of the cytoplasm (fig. 2*d*). The capsule cells were increased in number and prominence and some were swollen to twice normal diameter. The capsule appeared to be distended, often leaving a clear space around the cell in which an increased number of capsule cells were present. A few cells were greatly shrunken, and three or four empty capsules were found, possibly indicating complete disintegration. The nucleolus appeared larger than normal when simple swelling of the cell was present, and the nuclear membrane was then indistinct (fig. 2*a*).

In silver impregnation the neurofibrils were found to have undergone a process of simple condensation with an even darkening of the cytoplasm (fig. 2*c*). In some shrunken cells there was proliferation of subcapsular dendrites, and in a few others extracapsular branches were prominent.

The nerve fibres in the ganglia were uniformly beaded (fig. 2*e*), but none was seen in degeneration. The ventral nerve roots were likewise beaded but not degenerated. In frozen sections stained by Sudan III and Spielmeyer method no disorder of myelin was found within the ganglia. There were no changes in the interstitial tissue except that the fibrous capsules of the ganglion cells appeared more dense than usual. The vessels were normal.

The dorsal and ventral nerve roots in the lower lumbar and sacral region showed no cellular changes and the axis cylinders were intact throughout. In myelin stains an appearance of regular gaps of about 0·05 to 0·1 mm. in extent at each node of Ranvier was conspicuous (fig. 5*c*). In this situation there was no free fat or cellular reaction (fig. 5*d*). There was no Wallerian degeneration, and no evidence of damage to blood-vessels.

In the spinal cord the myelinated tracts and the myelin traversing the grey matter appeared unaffected. The nerve cells showed a remarkable degree of alteration (fig. 3). In many this appeared to be a profound degree of axonal reaction with the usual powdering of the Nissl substance and displacement of the nucleus to one side of the cell body (fig. 3*d*). In others the nucleus was not displaced but was either greatly swollen with indistinct margin and granular contents or stained very darkly with crenated edge (fig. 3*a*). These dark nuclei were particularly evident in hæmatoxylin and eosin sections, and the cell was usually shrunken at this stage. As a final stage the whole cell appeared to stain darkly (fig. 3*b*) though Nissl substance was often still present. An unstained halo surrounding the nucleus was common in the lesser degrees of change and perinuclear chromatolysis was present in all. In some cells there was an accumulation of dark yellow pigment lying outside the nuclear membrane, often in strange shapes (fig. 3 *c* and *d*). In a few cells the natural cellular pigment was increased in quantity, though never to any remarkable degree (fig. 3*b*). These changes were found in all cells of both dorsal and ventral horns of lumbar, thoracic and cervical segments, but were much further advanced in anterior horn cells. There was no gliosis though there appeared to be a mild swelling and prominence of astrocytes. Only

in one place were some six or seven lymphocytes found lying in a perivascular space. There was no meningeal reaction and the blood-vessels were not affected.

In the brain-stem all motor nuclei showed similar changes in nerve cells. Occasional damaged cells were found in other nuclei but were minimal in degree and frequency. No evidence of glial or vascular change was found. An occasional Purkinje cell showed nuclear enlargement and lack of definition, but otherwise the cerebellum was normal in every respect.

Sections of frontal, parietal and occipital cortical gyri stained with cresyl violet showed a normal cortical architecture, and revealed no abnormality other than an occasional darkly staining ganglion cell. There was a generalized prominence of oligodendroglia nuclei, many of which showed evidence of some swelling of cytoplasm, but only a very slight astrocytic reaction was present. There was no accumulation of histiocytes. The blood-vessels were not altered, and there was no sign of hæmorrhage or other extravasation. There was no evidence of meningeal irritation. Frozen sections of these regions stained by the Bielschowsky method also revealed no abnormality. The Spielmeyer method for myelin applied to similar sections, however, revealed the presence of pale areas in the white matter of both frontal and temporal gyri and even more distinctly in the central white matter near the ventricles (fig. 4*a*). Such areas were most usually around a small arteriole, itself showing no pathological change. The myelin immediately surrounding the vessel was also commonly unaltered (fig. 4*b*) whereas a wide outer concentric ring showed only occasional myelinated tubes, and these greatly swollen and irregular with a few droplets (figs 4*b* and 5*a*). Fat stains (Sudan) also showed these areas of pallor but failed to show any free fat. Nor were any fat granule cells present. Bielschowsky staining of the same areas revealed that though axis cylinders were not interrupted they were unduly pale and thin in each patch of demyelination (fig. 5*b*). This change is evidently that which was found by Baker and Watson (1945). No changes in myelin were found in the brain-stem or spinal cord. No changes were found in cerebral or spinal blood-vessels, nor was any degree of pigmentation found in or near them, or in the choroid plexus.

Discussion.

The very rapid recovery from severe delirium described in our first case is paralleled by the extraordinary recovery from a severe paralytic episode in the second patient who returned to his occupation for two years before his fatal attack. The development of bulbar symptoms is naturally a grave complication. Melkersson (1926) and Baker and Watson (1945) also record instances of recovery from paralysis with bulbar symptoms. The occurrence of convulsions has been noted by Campbell (1898), Harbitz (1924), Turner (1938), and others, and in our second case as in Turner's report marked a distinct phase in each attack. Indeed the whole evolution of the symptomatology of the second attack repeated that of the first. In the sequence of events the well-known abdominal cramps were characteristic. In our case the dilatation of the stomach regarded as primary by Barker and Estes (1912) was certainly absent. Radiological gastro-intestinal investigation failed to account for the pains.

Oliguria has also frequently been observed, and in our second patient had led to the erroneous conclusion that the first attack was a glomeru-

lonephritis. Indeed the kidneys showed terminally some mild but clear damage but this was unlike any of the usual kinds of nephritis. The oliguria occurred during the phase of rising blood-pressure. The typical burgundy colour of the urine developed late in the second attack. Since no adequate test was performed we are not able to deny the presence of porphyrins earlier in each attack. Waldenström (1939) has, however, recorded a case when porphyrins were absent in some attacks and present at a later date. He therefore maintains porphyrins as such play a relatively unimportant part in the development of symptoms. He notes that an acid urine is necessary to reveal their presence, even spectroscopically. Blum and Schumacher (1937) record a case that appears to be characteristic in every way, with, in addition, an abnormal cutaneous sensitivity to light, with negative spectroscopic test for porphyrins. If the entire absence of the pigments in some attacks is further substantiated the importance of recognition of the very characteristic clinical course of the nervous disorder becomes greater. In our first patient the continued excretion of porphyrins occurred after the burgundy colour of the urine ceased.

In our second case the burgundy colour was absent until near the termination. Such degree of unreliability of pigmentation of the urine as a diagnostic feature was a striking clinical lesson.

The pathological changes here recorded are undoubtedly identical with those patchy and slight affections which have been observed by others. When it is realized that the nerve trunk proximal and distal to each patch showed degeneration of only isolated fibres, and in many instances no change at all, one of the most remarkable features of the affection becomes manifest. For six days the patient had complete paralysis of the lower limbs except for some toe movements. The inability of Loeffler (1919), Rothman (1926), and Borst and Königsdorffer (1929) to find any change in samples of the nerves in their cases is recalled. In those instances the duration of severe paralysis had been very brief. Erbslöh (1903), Grünewald (1922) and Baker and Watson (1945) have however noted that except when very severe, the degeneration of myelin is patchy and not accompanied by destruction of the axis cylinders. Mild degrees of lymphocytic infiltration had been noted by Mason *et al.*, Palmer, and others, but is as scattered and inconstant as the other changes. The finding of lesions is therefore a matter of chance in the early stages, and intact myelin at one level does not exclude damage more proximally. Further Erbslöh (1903) noted that even when Wallerian degeneration was present in the femoral nerve the internal saphenous nerve, a sensory branch, failed to show any change.

In the interpretation of our own findings we would point first to the gaps in myelin at the nodes of Ranvier in the nerve roots as being very similar to those described by one of us (1944*a*) in segments of nerve rendered ischæmic by pressure. Such widening of the node is also found as an early stage of Wallerian degeneration, of which the other signs such as fragmentation of the axis cylinders were however absent. The lesions in the posterior tibial nerve moreover present further characteristic features of a more severe degree of ischæmic lesion, namely great irregularity of staining of myelin for lengths of 2 or 3 mm., and even absence of the sheath for 1 mm., without the formation of Wallerian ovoids, and with the resumption of normal myelin distal to the lesion. The axis cylinder is not interrupted. We identify this process with that we have described to result from prolonged experimental ischæmia (1944*b*). Finally the clinical manifestation of the ischæmic experimental lesion in moderate degree is motor paralysis with minimal or absent sensory change. This is the prominent clinical feature of porphyrinuric "neuritis."

Another feature of the intermediate degree of experimental ischæmic lesion consequent upon the preservation of intact axis cylinders is the absence of change in the electrical excitability of the paralysed muscles (Denny-Brown and Brenner, 1944*a*). In reported fatal cases of paralysis with porphyria, including our own, the total duration of paralysis is usually too brief for reaction of degeneration to have occurred. Ross and Bury (1893), however, note that in Landry's paralysis, without differentiation of the type due to porphyria, the electrical excitability of paralysed muscles frequently remained unaltered. Grünewald (1922) observed electrical reactions like those of myasthenia gravis in a typical case of porphyria with paralysis. Waldenström (1939) also observed a curious feebleness of movement that could be partly overcome by extreme voluntary effort. Such effects also indicate the incomplete nature of the lesion.

The peculiar nature of the lesions of central white matter, where myelin also undergoes dissolution without interruption of axis cylinders, appears to be entirely comparable to the ischæmic lesions of peripheral nerve. In the experimental lesion the cellular reaction is predominantly one of fat-filled histiocytes but these were not prominent before the tenth day, and both the central and peripheral lesions in our second case are younger than this. Small lymphocytic accumulations around vessels are common in experimental lesions in peripheral nerve after the third day.

The changes in nerve cells were of the same kind wherever they were found. The appearance of most cells was that of simple axonal reaction.

but the common occurrence of shrunken eosinophilic nuclei, often central in situation, presented a complication. It has been assumed by many that the accumulation of pigments within the cell is the mechanism of neural damage, and in some cases (Grünewald) even the cerebral glia has been laden with pigment. These pigments do not however appear to be directly related to the cellular damage in tissues such as the liver or kidney. In our own case, where the neuronal changes were as clear as any, pigmentation of the nervous system was not a factor. The only fatty change noted was the granular change in the cytoplasm of late stages of damage to nerve cells commonly found in many different conditions. Finally, the changes in the dorsal root ganglia were as advanced as those of any nerve-cells, in the absence of any impairment in general sensation.

We therefore cannot believe that the changes in nerve cells in this affection represent the primary feature of this disorder. They are a mixture of axonal reaction and the "vacuogranular" change of Cajal. The latter is found in many toxic conditions such as septicæmia, and its prominence in the present condition may indicate a special susceptibility of cells already in axonal reaction. We consider the homogeneous nuclear shrinkage of Marburg with eosinophilic change to be only an indication of the severity of the process. The complete recovery of our case, and of similar instances reported by others, from earlier severe paralysis, indicates that the cellular changes are for the most part reversible.

In view of these deductions we are led to the conclusion that the primary damage to the nervous system in porphyria is not a degeneration, but an impairment of myelin compatible with the occurrence of widespread patchy and intermittent ischæmia. The renal changes are also of considerable interest. They are certainly not those of parenchymatous lesion, and in the absence of any morbid anatomy of the blood-vessels are best explained by an hypothesis of severe intermittent ischæmia. This would also explain the finding of necrotic kidney lesions by Waldenström (1937) with lymphocytic reaction.

In many published records of idiopathic porphyria, and in our own cases also, a notable feature has been the phase of vascular hypertension. At first onset of the cramp-like pains the blood-pressure is low, but gradually mounts to higher levels to reach a maximum of 180 mm. at the onset of delirium. At this stage the convulsions appear. With the onset of peripheral motor weakness the blood-pressure usually falls. Baker and Watson (1945) describe in their case "areas of attenuation" in the retinal arteries, interpreted as "vascular spasm," in the hypertensive phase and disappearance of this phenomenon when the blood-pressure fell. Though

this condition was not specifically looked for in the two cases here reported, we have since had the opportunity of observing another patient in the phase of hypertension through the kindness of Dr. Joseph Ross of the Massachusetts Memorial Hospital, and saw small segments of beaded constriction in the retinal vessels. Waldenström (1939) had described attacks of transient blindness at this stage. There is therefore collateral evidence of localized vasoconstriction. If renal vasoconstriction is the immediate cause of the anuria it will be noted that this occurs very early in the symptom-complex, possibly indicating that the vessels of different organs are affected in turn, thus suggesting the presence of a factor acting directly upon blood-vessels, rather than a central or ganglionic mediation.

The abdominal cramps so common in this affection have been the subject of much speculation. Our second patient who suffered from these in characteristic form, showed no radiological evidence of gastro-intestinal disorder beyond a minimal degree of cholecystitis. The abdominal pains were poorly localized and varied in distribution. In our first patient the pain was felt in the back between the shoulders. The explanation of Mason *et al.* (1933) based on the changes in nerve cells of the sympathetic ganglia takes no account of the occurrence of the pains for a long interval, often weeks, before the onset of neuritic signs. We are therefore inclined to include the prodromal pains under ischæmic manifestations, and blame local periodic extreme vasoconstriction sometimes visceral, sometimes neural or ganglionic, for their occurrence.

If the clinical manifestations of acute idiopathic porphyria are the result of a vasoconstriction which is a primary feature of the condition, it follows that search for a vasoconstrictor substance present in the circulating blood in the early stage may be profitable, both in determining pathogenesis and treatment. Such a search has not been made. It has been reported, however, that small doses of porphyrins injected into animals causes a rise of blood-pressure and increase in pulse-rate, whether the animal is exposed to light or not (Hausmann, 1910). Large doses caused a fall in blood-pressure. The absence of porphyrins in the urine at the time of onset of symptoms indicates that some other substance precedes the condition known as acute porphyria. One case of paralysis of characteristic type has been reported following the administration of hæmatoporphyrin hydrochloride intramuscularly for four weeks (Thorner, 1937), though the drug was commonly used in the treatment of psychiatric conditions at that time without such complication (Benjamin, 1937).

Changes in nerve-cells identical with those described here were found

in the dorsal root ganglia in "Landry's paralysis" by Sweiger (1909) and Bauer (1909). It is clear that many cases of ascending motor paralysis are in reality porphyrinuric "neuritis" as was pointed out by Grünewald (1922). Most commonly the weakness begins in the upper limbs, and it is doubtful if the phenomenon of ascension is of any significance. Many instances of recurrent or relapsing motor neuritis such as were reported by Sorgo also probably belong to the same category. In view of the occasional reports of extensor plantar response in "porphyrinuric neuritis" and the central lesions demonstrated in this condition it would seem desirable to avoid the use of the term "neuritis," and particularly "motorneuronitis," in favour of the description of the condition as the nervous complications, or changes, of porphyria.

The fact that the appearance of porphyrins in the urine is not a necessary accompaniment of the nervous manifestations of the condition raises a question of considerable significance, for the condition typified by our first case is that of delirium tremens, by that of our second case, "acute infectious polyneuritis" with bilateral facial palsy but with low spinal fluid protein. Either the pathogenesis of all these conditions is that of a general toxic reaction, or there is an underlying metabolic dysfunction common to them all. We believe that the disorders are indeed specific, and represent a distinct type of neurological manifestation of metabolic disorder.

Conclusions.

Two cases of acute "idiopathic" porphyria are presented. In the first a brief delirium with tremor was followed by recovery. In the second the more usual abdominal cramps with delirium convulsions and severe motor paralysis occurred in two attacks separated by an interval of two years. The patient died in the second attack and pathological examination revealed lesions of ischæmic nature in the peripheral nerves and cerebral white matter. The possibility of presence of some locally acting vasoconstrictor substance is discussed in relation to the pathogenesis of the visceral disorders of porphyria. The importance of consideration of the condition in states of acute delirium with or without "toxic" motor neuritis is emphasized.

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DESCRIPTION OF FIGURES.

Fig. 1.—*a*, Posterior tibial nerve. Frozen section. Spielmeyer stain for myelin. To show the damaged myelin in a small area at the edge of a fasciculus, without degeneration. *b*, Posterior tibial nerve. Transverse section, cresyl violet. Note patchy œdema and normal vessels. *c*, Posterior tibial nerve. Longitudinal section, cresyl violet. To show cellular changes.

Fig. 2.—*a*, 5th lumbar dorsal root ganglion. Hæmatoxylin and eosin. *b*, 1st sacral dorsal root ganglion, cresyl violet. *c*, 5th lumbar dorsal root ganglion, Gros-Bielschowsky. *d*, As fig. 2b. *e*, As fig. 2c to show a bundle of nerve fibres traversing the ganglion.

Fig. 3.—*a*, Spinal cord, anterior horn at 8th cervical level. Hæmatoxylin and eosin. *b*, The same at 5th lumbar segment. *c* and *d*, Anterior horn, 5th lumbar segment, cresyl violet.

Fig. 4.—*a*, Central white matter of the right cerebral hemisphere. Frozen section, Spielmeyer method for myelin. *b*, The same, higher magnification.

Fig. 5.—*a*, The edge of a patch of demyelination in the central white matter, Spielmeyer method, to show the globular dissolution of myelin. *b*, The centre of one of the areas of cerebral demyelination stained by Gros-Bielschowsky to show faintly stained axis cylinders, a normal vessel, and increase of oligodendroglia. *c*, 1st sacral dorsal nerve root. Spielmeyer method. *d*, The same but stained with Sudan III and hæmatoxylin, and higher magnification.

THE E.E.G. IN THE PROGNOSIS OF WAR NEUROSIS.

BY MOLLIE E. HEPPENSTALL[1], DENIS HILL AND ELIOT SLATER

In 1941 Williams showed that the percentage E.E.G. abnormality in any group of men varied with the presence of certain traits of personality which are commonly found in those incapable of standing the stresses of military service. These personality traits were not defined, but their presence was clearly implied by the particular grouping which Williams used. Thus, of selected flying personnel 5 per cent. had abnormal E.E.G.s, of R.A.M.C. personnel 10 per cent., and of psychoneurotic individuals 26 per cent. In 1942 Hill and Watterson found 32 per cent. E.E.G. abnormality among psychopathic soldiers of the inadequate type and 65 per cent. among soldiers of the hostile aggressive type, the disorders shown by these men being of a more serious kind than the psychoneuroses.

In the same year the E.E.G. was used as a screening test for 274 candidates for entrance to the U.S. Army by Harty, Gibbs and Gibbs (1942). Knowing nothing of the clinicians' opinions they found that 55 per cent. of the men rejected on psychiatric grounds had abnormal E.E.G.s, compared with 28 per cent. of those accepted. Solomon *et al.* (1943) have stated that the E.E.G. was of primary value in deciding whether a man should be accepted for the U.S. Navy in 10 per cent. of 432 recruits. In a further 53 per cent. the E.E.G. contributed to the final decision.

A wider use of the E.E.G. as a method of screening entrants to the U.S. Armed Forces has also been advocated by Pacella (1943). If attention is paid to the specific epileptic wave forms alone, such screening, though costly in time and effort, might be useful; but it is clear that only about 25 per cent. of epileptics would be discovered by this method. However, the larger problem is whether the presence of a non-specific dysrhythmia should influence the judgment of a clinician who is considering the acceptance or rejection of an admitted neurotic, or should weigh against the retention of the man in the Service when he has broken down. The present investigation is an attempt to settle this problem.

We examined 300 soldiers who, having broken down with neurotic symptoms, were passing through a neurosis rehabilitation centre to new units in the Army. Their subsequent Army records were followed up by using the scheme controlled by the Ministry of Health by arrangement

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with the War Office. This follow-up information covered a period varying up to 15 months. It must be emphasized that these men had developed neurotic symptoms under conditions of service in this country; they had not experienced battle stress nor did they during the period of the follow-up. For this reason their illnesses must be regarded as having a predominantly constitutional ætiology. At the time of the E.E.G. analysis we had no information about the diagnoses, nor of course about the results of the follow-up.

These 300 records were analysed in detail by one of us (M. H.) and were subsequently placed in one of five groups by two of us (M. H. and D. H.). The five groups bear resemblance to those used by Davis (1941). Nine cases were discarded owing to the presence in the records of excessive artefact. Only one case had a specific dysrhythmia, thereby falling into the fifth of our five groups, and this man subsequently proved to be a traumatic epileptic. We were therefore left with 290 records divided among two normal groups, one doubtful group and one group with non-specific abnormality. Group 1 contained those whose E.E.G.s were undeniably normal: Group 2 those with E.E.G.s within normal limits, but with some minor variant, such as low-voltage fast or slow rhythms, with an incidence regarded as insignificant, or with instability to hyperventilation at fasting blood-sugar levels, as the only abnormality: Group 3 contained those whose E.E.G.s were regarded as doubtful; and Group 4 those with definitely abnormal E.E.G.s but with no specific abnormality such as a localized focus of abnormal potentials or paroxysmal outbursts of organized abnormal activity such as are commonly seen in epileptics.

In the detailed analysis observation was made of the following characters:—

(1) The alpha rhythm: its frequency, amplitude, symmetry and response to arousal stimuli.

(2) Rhythms at less than 8 c/sec. classified as individual frequencies, i.e. 1-2, 2-3, &c.

(3) Rhythms at more than 14 c/sec. classified as 14-16, 16-20, 20-24, and over 24 c/sec.

(4) The amplitude of any abnormal rhythm.

(5) Whether any abnormal rhythm was generalized or focal; if focal, its localization.

(6) The presence of an abnormal frequency as dominant.

(7) The response to hyperventilation.

We have not recorded the time during which any frequency was

present apart from noting the dominance of abnormal rhythms. Automatic frequency analysis would obviously have been of value in this investigation.

Results.

All the observation data were punched on cards and were sorted, counted and examined statistically by one of us (E. S.). This was done especially with a view to answering the question whether there was any significant association between any particular E.E.G. finding and the satisfactory or unsatisfactory nature of the follow-up record. Practically all the E.E.G. findings proved to have no such association. The most important data are embodied in Table I. It will be observed that, taking the group of patients as a whole, 13 per cent. had undeniably normal E.E.G.s (Group 1), 29 per cent. had normal E.E.G.s (Group 2), 34 per cent. had definitely abnormal E.E.G.s (Group 4), and 24 per cent. had doubtful E.E.G.s (Group 3). Fast rhythms were found in 18 per cent., slow rhythms in 46 per cent. Both fast and slow rhythms were found in 7·6 per cent. Only 0·7 per cent. had delta rhythm, while 58 per cent. had some degree of 4-7 c/sec. rhythm, many of these being classified as Group 3. 16 per cent. had rhythms in the 14-20 c/sec. band. 61 per cent. had an alpha rhythm at 9-10 c/sec.

From the point of view of the follow-up, the men could be classified into three classes: those who, when last heard of, were performing full duties; those who could only be employed on light duties; and those who had been invalided out of the Army at some time subsequent to their stay in our hospital. The data in Table I are accordingly classified in this way.

When these figures are tested by Chi squared, they are found to be, with two exceptions, distributed in a random manner between the three classes of men and there is no suggestion that normality or abnormality of E.E.G. record, or the presence of abnormal slow rhythms, is associated with a satisfactory or unsatisfactory Army follow-up record. Actually, it will be found that the E.E.G. Groups 2 and 3 did on the whole better than Groups 1 and 4; this difference reaches a low standard of significance (Chi squared for one degree of freedom = 4·8, probability of explanation by chance less than 0·05). The presence of abnormal fast rhythms does seem to be of bad prognostic omen, as there are more men with abnormal fast rhythms among the two bad follow-up classes than is at all easily explicable by chance (Chi squared for one d.f. = 5·57, P less than 0·02). It is of interest that if the combination of an abnormal E.E.G. record

TABLE I.—E.G.G. FINDINGS IN 290 NEUROTIC SOLDIERS CLASSIFIED BY SUBSEQUENT ARMY RECORD.

	Follow-up Record				
	Invalided	*Light Duty*	*Full Duty*	*Total*	*Per cent.*
Total patients	59	58	173	290	100·0
Of these :					
Normal E.E.G. (Group 1) ..	10	9	18	37	12·8
Normal E.E.G. (Group 2) ..	13	17	54	84	29·0
Doubtful E.E.G. (Group 3) ..	15	8	47	70	24·1
Abnormal E.E.G. (Group 4) ..	21	24	54	99	34·1
Cycles per Second :					
2– 3..	—	1	1	2	0·7
3– 4..	3	6	9	18	6·2
4– 5..	14	13	42	69	23·8
5– 6..	15	10	50	75	25·9
6– 7..	11	3	14	28	9·7
7– 8..	6	4	14	24	8·3
8– 9..	11	19	67	97	33·4
9–10..	33	35	108	176	60·7
10–11..	15	16	41	72	24·8
11–12..	3	1	12	16	5·5
12–13..	—	—	2	2	0·7
13–14..	—	—	3	3	1·0
14–16..	8	5	9	22	7·6
16–20..	5	5	15	25	8·6
20–24..	2	2	1	5	1·7
Over 24	—	1	1	2	0·7
Alpha rhythm :					
Symmetry	59	58	173	290	100·0
Voltage high	—	4	7	11	3·8
Voltage low	5	4	16	25	8·6
Inhibition persistent	1	2	2	5	1·7
Negative response to eye-opening ..	1	—	2	3	1·0
Abnormal rhythms :					
Fast	14	15	24	53	18·3
Slow	30	21	82	133	45·9
Both	5	6	11	22	7·6
Neither	20	28	78	126	43·4
Fast rhythms :					
Diffuse	14	13	23	50	17·2
Frontal	—	2	1	3	1·0
Parietal	—	2	1	3	1·0
Right	—	2	1	3	1·0
Left	—	2	1	3	1·0
As dominant	3	1	2	6	2·1
Voltage=dominant	4	6	6	16	5·5
Slow rhythms :					
Diffuse	28	17	68	113	39·0
Frontal	1	1	6	8	2·8
Temporal	—	—	3	3	1·0
Parietal	—	1	6	7	2·4
Occipital	1	—	2	3	1·0
Right	1	2	8	11	3·8
Left	2	3	9	14	4·8
As dominant	—	—	1	1	0·3
Voltage=dominant	27	19	71	117	40·3
Voltage>dominant	2	4	6	12	4·1

(Group 4) and fast frequencies is taken, the prognostic significance becomes still more marked. There were only 26 of these men altogether, but 9 of them were invalided, 9 were employed on light duties, and only 8 were on full duty (Chi squared for 1 d.f. = 9·9, P = approx. 0·002).

The actual rate of the alpha rhythm is of interest. The data are given in Table II. There is no indication of any difference in the rate of alpha

TABLE II.—RATE OF ALPHA RHYTHM IN 290 SOLDIERS, CLASSIFIED BY SUBSEQUENT ARMY RECORD.

Alpha Rhythm	*Invalided and Light Duty*	*Full Duty*	*Difference*
Mean	9·413	9·471	0·058±0·096
Standard Deviation ..	0·770	0·831	0·061±0·068

rhythm between the classes of men with poor and good outcome. It may be noted that the alpha rhythm rate was also examined in the groups of men with and without (*a*) abnormal fast rhythms, and (*b*) abnormal slow rhythms. No significant differences were found. These findings suggest that the alpha rhythm rate is not of great psychiatric significance among psychoneurotics.

A high proportion of these soldiers showed more than one frequency of rhythm, even when allowance was made for the fact that, for instance, a rhythm lying between 8·5 and 9·5 c/sec. would be punched on the card in both the 8-9 and 9-10 positions. The numbers of the men were counted who showed 1, 2 up to 5 different frequencies of rhythm. These numbers were, for all three classes of men taken together: 130, 110, 42, 6, 2. They form a Poisson series (Chi squared for 3 d.f. = 2·14; P between 0·7 and 0·5). This appears to indicate that an accumulation of rhythms at a number of different frequencies in any one record can be accounted for by randomly operating causes. This is in conformity with the fact that there were no significant differences between the three outcome classes in the means of the numbers of different rhythms exhibited per man. But there was a significant difference between the standard deviations of these numbers. In the light and invalided classes taken together, the S.D. was 3·8325, in the full duty class 3·2529 (difference = 0·5695 ± 0·2079, t = 2·74, P less than 0·01). This means that there is greater variability in the manner of distribution of energy among the prognostically worse classes than among the prognostically better, class compared with class. Put in still other words, it might be said that when the degree of "scatter" of energy is measured, the prognostically worse classes of men are more variable than the others in the extent to which they show this phenomenon. This observation falls into line with other observations of

a widely different kind that go to show the greater variability of the neurotic as compared with the normal in respect of agility, auditory and visual acuity (Slater and Slater 1944), and bodily habitus (Rees 1944).

SUMMARY.

Three hundred soldier patients in a psychoneurotic rehabilitation centre had their E.E.G. records taken. After their return to the Army they were followed up for periods up to fifteen months. Nine records were discarded owing to the presence of excessive artefact, and one record with a specific form of abnormality, which proved to belong to a traumatic epileptic. Of the remaining 290 men, 59 were subsequently invalided, 58 when last heard of were on light duty, 173 on full duty. Of the whole group 121 records were normal, 70 were doubtful, 99 showed a non-specific abnormality. There was no association between abnormality of E.E.G. and an unsatisfactory follow-up record. The presence of abnormal fast rhythms was associated with a bad outcome, and more definitely so if these rhythms were found in an E.E.G. record which was classified as non-specifically abnormal. The total number of men who showed this combination was less than 10 per cent. of the whole group. The alpha rhythm rate for the poor and good outcome classes showed no significant difference. In the total number of frequencies observed per man, the bad outcome classes showed a greater variability than the good outcome class. This can be thought of in connection with the greater variability of neurotics as compared with normals in respect of several other physical characteristics. It is concluded that the use of the E.E.G. in screening Army entrants, or soldiers who have suffered a neurotic breakdown, can only be engaged in with the utmost caution.

We have to thank Mr. J. Theobald for his invaluable assistance in taking the E.E.G. records and in other technical matters.

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THE ARTERIAL RELATIONS OF THE INTERNAL AUDITORY MEATUS.

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THE variable origin of the internal auditory artery from the basilar and anterior inferior cerebellar arteries is now well established (Stopford, 1916; Watt and McKillop, 1935). It would appear, however, that the unusual course customarily pursued by this cerebellar artery in relation to the internal auditory meatus and the manner in which this influences the site of origin and course of the internal auditory artery have passed unnoticed. This is due no doubt to the fact that observations on these vessels have in the past been limited to material which had been removed from the cranial cavity in the process of which gross disturbance of normal anatomical relationships is inevitable.

This paper records the topographical relations of the anterior inferior cerebellar and internal auditory arteries as observed in 264 dissections (132 subjects) in which the cerebello-pontine angle was exposed, by reflecting the tentorium, and examined in the undisturbed state. The findings are set out in the table on page 24 in which the neuro-vascular relations have, naturally, been reduced to their simplest forms. Variations are superimposed on these simplified patterns but they are of a minor character and in no way influence the subject matter of this paper.

The term 7th nerve refers throughout to both divisions. When the anterior inferior cerebellar artery passed between the nerves entering the internal auditory meatus, it did so, in most instances, between the main motor division and the portio intermedia. This point should be kept in mind throughout the ensuing description.

ANTERIOR INFERIOR CEREBELLAR ARTERY.

In 64 per cent. of all cases the anterior inferior cerebellar artery was related to the 7th and 8th nerves either within or at the mouth of the internal auditory canal. In approximately 22 per cent. of these the artery was small but in the remainder it was of large calibre. In only 43 specimens was the arrangement symmetrical.

In 39 per cent. of all cases the artery entered and descended along the internal auditory meatus ventro-medial to the 7th and 8th nerves after a

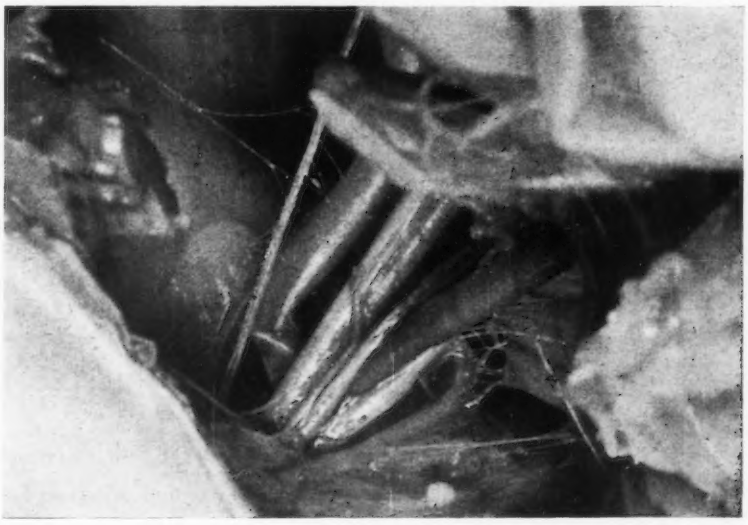
mildly curved or more tortuous course ventral to them in the cerebello-pontine angle. The artery descended for a variable distance along the canal beneath the nerves and, having reached the limits of its passage, looped and returned towards the orifice. In 7 specimens the recurrent limb of the arterial loop, while still in the canal, passed upwards between the 7th and 8th nerves and then coursed dorsolateral to them as far as

TABLE I.—RELATION OF THE ANTERIOR INFERIOR CEREBELLAR ARTERY TO THE AUDITORY MEATUS.

	R.	L.
(1) The artery passed between the nerves while coursing in the meatus	5	2
(2) The artery looped well down the meatus. The recurrent limb of the loop passed to the cerebellum between the nerves well medial to the meatus ...	43	39
(3) The artery entered the meatus but the recurrent limb emerged and passed to the cerebellum below the nerves	5	7
(4) The artery entered the meatus but the recurrent limb came to lie entirely above the nerves ...	2	0
(5) The artery just looped into the mouth of the meatus while the recurrent limb of the loop passed to the cerebellum between the nerves well medial to the meatus	16	13
(6) The artery just looped into the mouth of the meatus while the recurrent limb of the loop passed to the cerebellum below the nerves	19	17
(7) The artery passed between the nerves without establishing a relation with the meatus	6	6
(8) The artery passed to the cerebellum immediately below the nerves without establishing a relation with the meatus	8	12
(9) The artery, after coursing laterally anterior to the nerves, passed to the cerebellum immediately above them without establishing a relation with the meatus	2	2
(10) The artery was absent, or was not related significantly to either the nerves or the meatus ...	26	34
Total number of specimens examined	132	132

the aperture from which point it passed posteriorly to the cerebellum. In 82 specimens the recurrent arterial limb passed between the nerves after the vessel had left the canal and was again lying in the cerebello-pontine angle. In 8 of these 82 specimens a branch of the artery and not the main trunk ascended between the nerves just medial to the meatus, while in an additional specimen the ascending perforating branch was derived

from the proximal limb of the loop as it entered the meatus. In these 9 specimens the main trunk of the anterior inferior cerebellar artery continued posteriorly below the nerves to reach the floccular region of the cerebellum. On twelve occasions the recurrent limb retraced its course in the canal below the nerves and continued in that relationship to reach the cerebellum. In two specimens the artery entered and descended along the canal as described and then folded over the nerves to lie superior to



The left cerebello-pontine angle has been exposed from above after the tentorium has been reflected and the cerebellum displaced inwards and backwards. The 7th and 8th nerves are shown passing to the internal auditory meatus and the loop of the anterior inferior cerebellar artery is shown presenting into the mouth of the canal after having been withdrawn from it when the cerebellum was displaced. The returning limb of the arterial loop is seen passing between the 7th (both divisions) and 8th nerves while the internal auditory artery has branched from the anterior inferior cerebellar artery on the pons.

them. The recurrent arterial limb then returned above the nerves and on regaining the cerebello-pontine angle turned backwards over them to reach the cerebellum.

In 25 per cent. of the specimens examined the arterial looping described above only just reached the orifice of the canal into which the apex of the arterial loop projected ventro-medial to the contained nerves. In 29 of these specimens the recurrent arterial limb passed between the 7th and

8th nerves on its way to the cerebellum while in 36 it passed to its destination beneath them. In some cases unusual and complicated loopings in the vicinity of the orifice of the meatus increased the complexity and intimacy of the neuro-vascular relations at that site.

In the remaining 36 per cent. of all cases the anterior inferior cerebellar artery was absent or was not related to the meatus.

Internal Auditory Artery.

In approximately 17 per cent. of the specimens the internal auditory artery took origin independently from the basilar artery and entered the meatus as a separate arterial channel anterior to the 7th and 8th nerves.

In the remaining 83 per cent. the artery took origin from a variable point on the anterior inferior cerebellar artery. When the latter looped into the meatus or well down the canal the auditory artery arose, in most instances, from the apex of the loop, occasionally from the proximal limb at points between the pons and the apex but never from the recurrent limb. Its course is apparently determined by the position of the proximal limb and loop of the anterior inferior cerebellar artery.

Duplication of the auditory artery was observed but was infrequent—when present it occurred as paired branches from the basilar or anterior inferior cerebellar arteries and infrequently as a single branch from each of them. The origin from the basilar artery was symmetrical in only 14 subjects.

Stopford (1916) gives the source of the internal auditory artery as follows:—

	Right	Left
Anterior inferior cerebellar artery.	64 per cent.	62 per cent.
Basilar artery	36 per cent.	28 per cent.

Watt and McKillop (1935) described an independent origin for this vessel from the basilar in only 3 out of 60 cases while Cavatorti (1908) observed such an origin on the right in 70 per cent. and on the left in 67 per cent. of his cases. In the remaining cases in both series the artery took origin from the anterior inferior cerebellar artery.

Thus it may be concluded that, with the exception of Cavatorti's observations, the evidence favours a predominant origin of the internal auditory artery from the anterior inferior cerebellar artery even though the reported frequency of such an origin varies.

Comment.

The intimate relationship of a large arterial channel to the 7th and 8th nerves in such a confined space as the internal auditory orifice and canal are anatomical features of more than academic interest.

The knowledge of such a relationship is of considerable practical importance in surgical explorations of the cerebello-pontine angle and in connection with certain disturbances of nerve conduction which may possibly arise as a direct consequence of mechanical pressure exerted on the nerves by atheromatous, enlarging, abnormally pulsating or tortuous vessels.

SUMMARY.

The neuro-vascular relationships of the internal auditory meatus have been studied in 264 dissections (132 subjects).

In 64 per cent. of the specimens examined the anterior inferior cerebellar artery was intimately related to the 7th and 8th nerves either within or at the orifice of the internal auditory meatus. These topographical relations have been described. In the remaining 36 per cent. the artery pursued a variable course unrelated to the meatus.

In approximately 17 per cent. of the specimens the internal auditory artery took origin independently from the basilar artery. In the remainder, 83 per cent., it arose from the anterior inferior cerebellar artery.

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VASCULAR DISEASES OF THE NERVOUS SYSTEM.

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PART I.

Introduction
The physiological control of cerebral circulation
Cerebral vasoconstriction in migraine
Cerebral vasoconstriction in cerebral type of hypersensitive carotid sinus
Cerebral vasodilatation
Functional vascular reaction productive of lesion
Hypertensive brain disease associated with softening
Cerebral softening predicated on cardiac weakness
Cerebral embolism
Cerebral thrombo-angiitis obliterans
Vasoparalysis
Discussion

PART II.

Cerebral hæmorrhage
Circulatory factor in spinal cord disease
Circulatory factor in peripheral nerve disease
Surgical implications
Summary

PART I.—INTRODUCTION.

A STROKE, usually differentiated (Aring and Merritt, 1935) as a cerebral hæmorrhage, thrombosis, or embolism, is commonplace and seemingly straightforward enough in its evolution. Strokes form the bulk of neurological admissions to any large civilian general hospital. Because this is so and because I have spent a considerable time in large general hospitals I am interested in strokes. There are other reasons for this interest: not the least is the fact that devotion to teaching the alert student and house officer and participation in clinical research does not allow any problem relating to illness, however commonplace, to lie fallow.

The cultivation of a large vascular material has made us rather dubious of the supposed simplicity of these lesions, particularly as it was usually found that the demonstration of a leaking or occluded cerebral vessel in pathological studies of the ordinary types of cerebral hæmorrhage or thrombosis, was fraught with great difficulty. This has held true despite

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careful search, and we were encouraged to learn that this experience is by no means unique.

Such being the case we turned to the cerebral vascular reactions for enlightenment. We would like to know whether or not disturbed vasomotricity of the cerebral vessels of man leads to tissue damage or death, and by what mechanisms apoplexy may be initiated. If these points can be reasonably determined, prophylaxis and therapy would not seem beyond attainment.

I would like to summarize our observations on cerebral vascular disorders, and draw freely on those of others.

The Physiological Control of Cerebral Circulation (Forbes, 1940).

We may lead up to the discussion with an outline of the physiological control of cerebral circulation. From the evidence provided by animal experimentation it seems that the neurovascular mechanism is a rather weak mechanism, not likely to participate in a process resulting in permanent damage to nervous tissue. Even though this may be a valid opinion, it should not be forgotten that there are avenues other than nervous for affecting changes in the calibre of cerebral vessels. These are (1) the presence of chemicals or drugs within these vessels; (2) pronounced changes in blood-pressure; (3) local activity of groups of neurons, which may obtain adequate circulation by a demand system; and (4) changes in resistance to flow within cerebral capillaries and venules, as in extreme dehydration or hydration. Œdema of the parenchyma tends to narrow capillaries and venules by restriction; dehydration encourages their dilatation.

Of considerably greater importance in the regulation of normal cerebral blood flow is the systemic arterial pressure, and the intracranial venous pressure. What happens to the total cerebral blood flow in the last analysis depends on factors largely extracerebral. This fact is never to be lost sight of in clinical considerations.

With this survey of the physiological factors regulating cerebral circulation in mind one may proceed with the evidence for cerebral vasoconstriction and dilatation, particularly in man.

Cerebral Vasoconstriction in Migraine.

The prodromata of migraine induced experimentally.—The neurological prodromata of migraine are well known and probably need no description. They are likely to be personally familiar to as many as 10 to 20 per cent. of any group. The visual phenomena, which have been

described under the terms of teichopsia and scintillating scotoma are the most familiar. Other less common neurological phenomena precedent to the headache of migraine are the pins and needles sensation, which may leisurely ascend an extremity and be followed by transient numbness; dysphasia is a less common precedent sign. Practically any lobe of the cerebrum, and even the cerebellum, have been involved in the prodromata of migraine. Rarely, permanent neurological disorders have occurred in the wake of migraine.

Shrewd evaluations concerning these phenomena have been made over the past century, particularly by physicians who suffered from the disease. Many were inclined to think that temporary alterations in blood-vessels had something to do with their origin. Wolff and his co-workers (1941), who have done so much to elucidate the dynamics underlying migraine, noted the apparent relief of the fleeting neurological prodromata with cerebral vasodilators such as amyl nitrite. Therefore these symptoms seem likely to be due to localized vasoconstriction.

The visual prodromata were analysed further at Cincinnati where Engel, Webb, Ferris, Romano, Ryder and Blankenhorn (1944) at the College of Medicine working with simulated high altitude noted that visual symptoms and headache were not uncommon manifestations of decompression sickness. The visual symptoms were exactly similar to those suffered by migraine victims and were usually followed by headache. They tended to occur repeatedly in certain subjects and not at all in others. The subjects of these experiments were 10 physicians, aged 28 to 57, 41 medical students, aged 23 to 30, and 104 University students, aged 17 to 26. 17 of these 155 subjects, with a series of 1,361 exposures at 30,000 to 38,000 feet, experienced scotomas a total of 46 times and, of the 17, 5 had more than one episode. Statistical study suggested that the occurrence of the syndrome following decompression sickness was at least partially determined by a predisposition to migraine.

The course of scotoma and field defects is difficult to predict and the effects of vasodilator drugs in this experimental group was inconclusive. Another method of evaluating the happenings within the cerebrum during these phenomena is with the aid of the electroencephalograph, simultaneous to charting the visual fields. Persons subject to the scotoma-migraine syndrome on previous flights of simulated high altitude were utilized and in several instances success was experienced in the induction of an attack. The electroencephalogram which had been normal previously became abnormal in the occipital lead over the lobe from which the visual disorder was emanating.

The development of this syndrome may be illustrated by a typical case.

Five minutes after reaching ground level after a flight at 30,000 feet lasting one and one-third hours, during which he had had bends and chokes, one subject developed scintillating scotoma and blurring of vision in the left field, and slight scintillation in the right upper quadrant. The transparietal lead continued to record normally, but sustained, slow activity of a frequency of 4 to 7 per second appeared in the right occipital lead. Within nineteen minutes there were scintillating scotomas in both fields with restriction of both fields of vision and considerable low voltage activity in both occipital leads.

Thirty-two minutes after onset, the scintillation and field defect on the left had receded to the upper quadrant. The right homonymous field defect was slightly less extensive. At this time the right occipital lead recorded only a small amount of 6 to 7 per second activity; the left occipital contained a dominant somewhat irregular 4 to 7 per second activity.

Forty-five minutes after onset of the visual phenomena the left visual field was normal, and scintillation and homonymous field defect were still present in the upper right quadrant. The subject now experienced the onset of bilateral frontal headache which within ten minutes was severe and was accompanied by nausea, vomiting, and defæcation.

One hundred and fifteen minutes after the onset there was intense throbbing headache and nausea, and no visual defect. The electroencephalogram had returned to the essentially normal original pattern. The headache disappeared five hours after its beginning.

Thus one may measure electrical abnormalities originating in the visual cortex corresponding to the localization of the homonymous visual field disturbances. Since the changed electrical activity consisted of decreased frequency without corresponding increase in amplitude, it appears that a decrease in cortical metabolism is responsible rather than some type of focal discharge phenomena. This indicates a phenomenon rather different from a convulsion, where cerebral metabolism is heightened, as indicated by oxygen tension studies in animals (Davis, McCulloch and Roseman, 1944), and where the electrical output is usually increased in amplitude. Obviously the intense headache is not of intracerebral origin since the electroencephalogram returns to normal during the period of headache.

Spontaneous prodromata of migraine.—Argument that these effects may not have been those of true migraine were disposed of when three of the University staff obligingly came down spontaneously with scintillating scotoma long enough precedent to the headache of migraine to obtain electroencephalographic studies. Rapidly placed electrodes recorded the fact that the affected occipital lobe in migraine was behaving exactly as that in the syndrome induced by decompression sickness.

This represents the best evidence extant that in disease of man spontaneous vasospasm may occur locally within a lobe of the cerebrum and

produce signs. One has no idea how long the spasm lasts, presumably it must be extremely transient and also relatively mild since irreversibility is rarely met.

Neither does one know why such selective topographical involvement occurs, but a host of examples of spontaneous and local vasomotor phenomena come to mind: such as that occurring in blushing, in angina, in Raynaud's syndrome, where it may be present in a portion of one finger, and in the stomach and nose in Wolff's experiments (Holmes, Wolff and Goodall, 1944: Wolf and Wolff, 1943).

Cerebral Vasoconstriction in Cerebral Type of Hypersensitive Carotid Sinus (Engel, Romano and McLin, 1944: Ferris, Capps and Weiss, 1935).

In this type of carotid sinus hypersensitivity, syncope may be followed by unilateral fits, or focal neurological signs and symptoms may develop without fall in blood-pressure or much involvement of consciousness. It is in the latter type that electroencephalographic data are particularly enlightening, since in it slow waves arise from the hemisphere corresponding to the cerebral signs. When unconsciousness supervenes the slow waves arise diffusely and if local clinical signs then occur no further change takes place in the electroencephalogram.

Despite the maintenance of normal total cerebral blood flow during the manifestations of the hypersensitive carotid sinus, clinical and cerebrospinal fluid studies (dynamics) indicate that some cerebral vasoconstriction occurs. Vasoconstriction may occur in local cortical areas without altering the total cerebral blood flow (Ferris, Capps and Weiss, 1935).

It remains for someone to chart visual fields during the stimulation of the hypersensitive carotid sinus of the cerebral type: presumably they will be affected and thence the phenomenon could reasonably be related to the prodromata of migraine.

Cerebral Vasodilatation.

We have obtained evidence of a dilator mechanism in certain intracranial vessels in man from measuring cerebral blood flow by the technique devised by Ferris (1941). Briefly the method consists in the measurement of the rate of cerebrospinal fluid displacement through a large lumbar puncture needle during sudden compression of the veins of the neck for a few seconds. The principle is similar to that utilized in the plethysmographic measurement of blood flow in the extremities. In our experiments the rigid cranium serves as the plethysmograph. Compression of the neck veins is effected by sudden inflation of an especially designed rubber cuff

surrounding the neck. With the use of a constant occlusive pressure (60 mm. of mercury) in the cuff and a constant cerebrospinal fluid pressure (200 mm. of water), the cerebrospinal fluid displacement rate in a given experiment bears a constant relation to the total intracranial blood flow. In other words with the venous outflow of the brain halted, any immediate increase in volume within the cranium must represent inflowing blood; an estimation of the latter is the amount of cerebrospinal fluid displaced.

In our hands (Aring, Ryder, Roseman, Rosenbaum and Ferris, 1941) nicotinic acid increased cerebral blood flow while no significant change occurred in the systemic blood-pressure, which must indicate an active dilator effect of this substance on certain intracranial vessels. The increased intracranial flow parallels the flushing of the skin observed with the administration of nicotinic acid and lasts from twenty to sixty minutes.

Direct observation of the pial vessels of the cat has revealed (Moore, 1940) that they widen after an injection of nicotinic acid.

Functional Vascular Reaction Productive of Lesion.

Experimental cerebral embolism.—The most convincing experimental evidence that functional vascular change may result in cerebral lesions in animals is the exhaustive study of Villaret and Cachera (1939) on the production of cerebral embolism in the dog. By way of a skull window they photographed the pial vessels with magnification. Observations were made from the time of embolization up to three hours, and later observations from 1 to 123 days after embolization.

The immediate reaction to solid emboli (finely pulverized marble or glass 80 to 150 microns in diameter, into a carotid artery) was widespread vascular spasm, as marked in fields where there were no emboli and therefore reflex in nature.

Typical spastic phenomena were intermittent and constantly recurring and were seen months after embolization. Spasm and dilatation sometimes co-existed in parts of the same vessel; changing calibre would recur over and over again within a few minutes. The dilated portions of vessels contain cyanotic blood indicating stasis and hypoxia. These experimenters noted that vessels affected by disturbed vasomotricity need not belong to the same parent vessel or vascular tree.

The venous effects were much more widespread than the arterial, and were generalized in practically all parts of the visible venous supply even though there was only one or two foci of arterial obliteration. The distension of veins was tremendous and the flow reduced to a thin trickle of blood, or there was tremendous engorgement of veins with arterial

blood which pulsated as in arteries. In many cases the venous flow was reversed.

In this study Villaret and Cachera also recorded photographically the sequential development of cerebral infarction, usually hæmorrhagic in the early stages, and of cerebral hæmorrhage. The latter was on occasions petechial or of the nature of hæmorrhagic infarction, on others it was gross, or there were combinations thereof; blood sometimes filled the ventricular system. This portion of their experiment will be referred to again in Part II, when cerebral hæmorrhage will be discussed.

In contradistinction to solid emboli, air emboli did not cause vasomotor disturbances and resulted simply in obstruction and its consequences.

With this evidence of cerebrovascular motor phenomena in mind, we may proceed to a consideration of some cerebral vascular diseases, and attempt to determine the plausibility of relating the one to the other.

Cerebral vascular accidents.—Attention may first be directed to the cerebral vascular accidents, or strokes or shocks as they may be termed. We have had a most liberal material which has been closely studied to include clinical, physiological and pathological aspects of the problem. The rarity with which gross occlusion of blood-vessels or gross breaks in them may be found within the parenchyma of the nervous system in cerebral softening or hæmorrhage has been noted; this has been the experience of several investigators. Thromboses are liberally distributed in such a condition as the cerebral form of thrombo-angiitis obliterans, about which more will be said shortly, but not in the ordinary clinical syndrome of cerebral softening. This paucity of rupture and occlusion of intraparenchymal vessels may be demonstrated in the brain disease associated with hypertension.

Hypertensive Brain Disease Associated with Softening.

The brain disease associated with arterial hypertension may be utilized as an example of a situation particularly prone to result in cerebral softening (termed clinically cerebral thrombosis); although such patients are more likely to succumb ultimately to cerebral hæmorrhage. Thus hypertension appears to be a precursor either of softening or hæmorrhage. Successive strokes may occur in association with hyperpiesis, and the patient appears to make a fair recovery therefrom. Possibly the state of affairs defined rather vaguely as hypertensive encephalopathy belongs within the realm of "stroke."

The hypertensive hyaline arteriolopathy which appears to repre-

sent one of the final physical concomitants of the clinical symptomatology of this disease is extremely rarely associated with thrombosis of vessels (Scheinker, 1943). However, there are small areas of softening of varying age scattered throughout the nervous parenchyma, contiguous or in relation to hyalinized arterioles, which suggests, as does the sudden onset of localizing and generalizing brain signs clinically, that cerebral softening has occurred repeatedly.

How may one reconcile the paucity of vascular occlusion on one hand with multiple softening on the other?

There would seem to be little doubt that much of the parenchymal change is secondary to the hyalinization and fibrosis of arterioles. The finding of relatively fresh parenchymal lesions among those of greater age would appear to preclude absorption of thrombi in vessels to explain their paucity. It would seem that this vascular lesion may interfere with the regulation of cerebral circulation in local areas and that the development of functional vascular phenomena is encouraged. The latter will be discussed further when we consider cerebral hæmorrhage.

On the other hand hyalinization may be the end-result of continued constrictor irritation as has been suggested by the work of Nedzel (1943) who produced comparable changes in the smaller blood-vessels in the brains of dogs with pitressin given weekly for a period from one to three years. He also produced focal areas of parenchymal destruction by this technique.

One might infer that the dynamics of such diseases as syphilis and arteriosclerosis, which may be associated clinically with the syndrome of cerebral softening, may be comparable with that of hyperpiesis. The arteries involved in these conditions are larger in calibre than those affected in arterial hypertension. Nevertheless the gross or microscopic finding of complete occlusion of a large vessel is a rarity, regardless of the length of the period of survival after the onset of apoplexy. The occurrence of softening strictly limited to the tissues supplied by a major artery would preclude the likelihood that one had missed the thrombus if it had been present.

The usual mode of onset of cerebral softening clinically is quite rapid (Aring and Merritt, 1935), a point not widely appreciated. Such an onset may be explained by vasospasm or by vasodilatation, either of which promptly interferes with the nourishment of a local area of the central nervous system. The rapid and remarkable recovery from a non-hæmorrhagic stroke associated with hypertensive encephalopathy, and the occasional prompt recovery in some elderly persons not particularly hyper-

tensive may be explained, if the concept of relatively rapidly reversible vasospasm is allowed. An alternative explanation will be discussed later.

The hæmorrhage occurring in association with hypertensive brain disease will be discussed in Part II which will be primarily concerned with cerebral hæmorrhage.

Cerebral Softening Predicated on Cardiac Weakness.

There are cases of local cerebral softening ascribed to changes in the peripheral circulation and the heart, which may be a *modus operandi* in hypertensive brain disease. This sequence is by no means as rare as may be thought. In most if not all of such cases there is as a rule well-developed cerebral vascular disease associated with cerebral arteriosclerosis (plaque formation in large vessels) (Fleming and Naffziger, 1927), hyperpiesis (arteriolar hyalinization and perivascular fibrosis), or other conditions (thrombo-angiitis, obliterative arteriolar sclerosis) in which there occurs hypertrophy of vessels, particularly arterioles and arteries, and consecutive narrowing of their lumina. Such cerebral vascular change need not, and indeed usually does not, manifest itself with symptoms, until the addition of cardiovascular disorder, usually functional and transient, further prejudices circulation to local areas of brain supplied by the diseased vessels.

Transient attacks, particularly characterized by vertigo and general weakness, may lend a clue before the onset of "stroke." These evanescent attacks may be somewhat analogous to the vasodepressor type of carotid sinus syncope.

There follows an abstract of the record of such a patient.

A 70 year old man (Case 114115) had been attending the clinic for four years because of anginal attacks, sometimes occurring as frequently as four times a day. His blood-pressure was maintained around 210/140, as far as it was determined.

With the final anginal attack, twenty days before death, there occurred a left hemiparesis which slowly (days) progressed to hemiplegia.

At autopsy numerous areas of old and new infarction were found in the heart and there was arteriosclerosis of its vessels and those of other viscera. In the brain there was tremendous hypertrophy and scarring of the subendothelial portion of the intima of arterioles. In the late stages cells had disappeared from the vessel lesion, leaving a mesh of fibrils which markedly narrowed the lumen. Small areas of softening of the parenchyma had occurred, the most recent in the right mid-brain. The large vessels of the circle of Willis showed ordinary arteriosclerosis. Nowhere could thrombosis be demonstrated.

It is obvious that this vascular change, which we have termed obliterative arteriosclerosis, had been present for a long period of time, since a stage of scar formation had been reached in the lesions of the arterioles.

These vessels evidently performed their function even though diseased, until finally myocardial infarct interfered long enough with cerebral circulation to result in mid-brain softening. Possibly previous circulatory interferences of equal duration were not deleterious because enough vessels remained, the lumina of which delivered the required quota of nutriment, or areas not as vital as those in the mid-brain were destroyed. But there comes a point beyond which neither the fibrosis of arterioles or the cardiac inefficiency may go without causing local cerebral softening.

Cases of pontine softening come to mind, in which attacks of bradycardia and vertigo preceded for a year or more the onset of apoplexy and in which large plaques of arteriosclerosis impaired the circulation in the basilar artery but did not completely occlude the vessel. Post-mortem examination demonstrates the narrowness of the lumen and the parenchymal destruction. Functional cardiac change is not demonstrable at autopsy, and even though there may be evidence for it during life, everybody appears to be willing to close the matter with the finality of cerebral thrombosis.

Such cases as these suggest that the passive therapy of cerebral softening might be improved upon, even in the presence of the impaired circulation. Certainly this is so for the prodromal symptoms where the vasodilators, nicotinic acid and whisky, should be used liberally, possibly even in the attempt at prevention.

Cerebral Embolism.

In the light cast by the important studies of Villaret and Cachera might the time not be propitious to revise some of our pathological tenets concerning cerebral embolism? The capriciousness of this disorder immediately comes to mind: it is at once the most and the least severe, and the most and the least recoverable of the apoplexies. It is the most suddenly occurring stroke and is not preceded by prodromal cerebral symptoms.

In some cases the clinical signs, at first extremely severe, may disappear with unexpected and dramatic rapidity and complete recovery ensue. In others a complete hemiplegia rapidly clears within a few days leaving behind weakness of movements about a single joint on the affected side. Finally there are cases which never show improvement after the ictus.

It has been thought that an embolism adherent to a portion of the vessel wall might retract away from the wall elsewhere and reopen the blood channel, thereby relieving signs in those cases in which this sequence of events presumably occurred.

It is probably more reasonable to consider the clinical signs as due to the widespread functional vascular disorder that accompanies the lodgment of a solid cerebral embolus, and to attribute the dramatic recovery to the reversibility thereof. Such a formulation allows at the same time for the ictal onset without cerebral prodromata, for the dramatic recovery of some cases (rapid reversibility of disturbed vasomotricity), and for the relatively complete lack of recovery of others.

It may be seen why multiple emboli, as in cerebral fat embolism, allow little or no chance of recovery. Evidently a solid embolus is the stimulus which calls forth the most immediate, though of itself not necessarily the most deleterious, disturbance of the vasomotor control of cerebral vessels.

Cerebral Thrombo-angiitis Obliterans.

On a number of occasions we have followed this disease through the clinic and histopathologically (Aring, 1944: Scheinker, 1944*b*). The fixed lesions of cerebral thrombo-angiitis obliterans are comparable to those observed in the lower extremities, where advanced intimal proliferation occludes vessels.

In chronic cases of progressive nervous diseases, as for example, disseminated sclerosis, hypertensive encephalopathy, and the condition now under discussion, it is always possible in histological studies to unearth lesions which are relatively young and therefore of recent development. To those familiar with the clinical course of these diseases this point need not be laboured.

Considerably more information is to be derived from a study of fresh than of older lesions. The latter is a scar, and would accordingly be expected to guard its secrets.

Let us try to follow sequentially the lesions of cerebral thrombo-angiitis obliterans to see if by this method we may learn something about their development. What appears to be the earliest lesion is intramural hæmorrhage of small arteries, confined to subendothelial tissue and muscularis of an otherwise structurally normal vessel. The cells of the subendothelial portion of the intima are destroyed; those of the muscularis are swollen and beginning to disintegrate. The adventitia is preserved. In a later stage the blood is absorbed and fibroblastic proliferation has occurred. Macrophages are present in the area of hæmorrhage. The lumen of the vessel is encroached upon but not occluded in these early stages. However, the subendothelial portion of the intima continues to proliferate and eventually the vessel is occluded. It may then recanalize.

Focal parenchymal lesions of varying age may be found in the central nervous system secondary to the vascular occlusion.

Though the late stage of thrombo-angiitis obliterans represents classical thrombosis, it is of interest to speculate on the mechanism underlying the intramural bleeding. One may do this only with the aid of the clinical picture.

The earliest signs of cerebral thrombo-angiitis are focal and transient. Weakness, numbness, dysphasia, visual disturbances, and attacks of unconsciousness or convulsions may recur evanescently for years before the clinical picture becomes established. Such a history is reminiscent of hypertensive brain disease.

In cerebral thrombo-angiitis obliterans it is conceivable that repeated and relatively prolonged vasospastic and vasoparalytic phenomena may be associated with bleeding into the vessel, as well as with transient clinical signs. Transient spasm of retinal arteries has been observed in systemic thrombo-angiitis obliterans. Early in the course of the disease the symptoms and the vascular disorder are apparently reversible. It appears that the intramural hæmorrhage may be the precursor of the fixed lesion.

Vasoparalysis.

Now let us consider thoroughly the vascular change which has been designated vasoparalysis (Scheinker, 1944*c*), and those clinical conditions with which this functional disorder of small blood-vessels may be associated.

It is a physiological principle that a period of vasospasm is always followed by one of vasodilatation. If this abnormal reaction is unrelieved, paralysis of the vessel supervenes. There is diminished blood movement through either constricted or dilated vessels, the result of which is hypoxia, both of the vessel wall and the parenchyma supplied by the vessel. As Landis (1928) has shown, hypoxia may of itself result in increased permeability of capillary walls, first to fluid and later to protein. Diapedesis of cells may follow if the paralysis does not reverse. Under these conditions blood cell extravasations in any tissue occur from capillaries and venules and not from arterioles: certainly this is initially so. Bleeding occurs in multiple foci and almost simultaneously, and there is sometimes coalescence of hæmorrhage. Partial and then complete vascular stasis may develop in the local area. The ætiology of this disturbance of vasomotor control of cerebral vessels is now known.

Cerebral death occurs occasionally in persons in whom no structural change may be demonstrated in blood-vessels, but in whom areas of focal

necrosis of the brain, as well as hæmorrhagic softening and ischæmic nerve cell degeneration testify to the fact that derangement of the cerebral circulation has occurred. The disorder appears to be stimulated in a number of ways; hæmorrhagic softening associated with trauma or other factors; encephalopathy following sulphonamide ingestion or the administration of arsenical compounds; an acute type of cerebral death without apparent precipitating factor in infants; and a more lingering type of cerebral disaster in young adults are cases in point. Children previously well may be seized with the sudden onset of what appears to be encephalitis, or a young adult with a monoplegia.

We note this acute vascular disability as vasoparalysis and, like Ricker (1919), have deduced from a static histopathological picture some dynamic concepts. Much experimental work supports this hypothesis, derived essentially from pathology, none more than that of Villaret and Cachera which has been summarized above.

Occasionally children who have always been well develop a fatal acute cerebral syndrome without apparent cause. For want of a better explanation and because cerebral arteriosclerosis cannot reasonably be invoked as a cause, as it is so readily in adults, an equally vague reason is invoked, namely encephalitis.

We have been extremely interested in such cases and have accumulated evidence that they are brought to death by way of physiological cerebral vascular change.

Two children (Cases 172366 and 195994), aged respectively 2 years, and 5 months, had been quite well before the acute onset of vomiting and drowsiness in the older, and of irritability in the younger. The former rapidly went into status epilepticus and died about fifty hours after the first symptom, the temperature rising gradually to a height of 105 F. The younger child rather quickly developed hyperthermia, and some convulsive movements were observed throughout the hospital course of twelve hours. When these children sickened and died, Cincinnati was in the midst of prolonged heat waves.

Grossly the central nervous system of the older child revealed cerebral œdema, characterized by tremendous increase in bulk of the white matter with secondary compression of the cortical ribbon and ventricular spaces.

The brain of the younger child disclosed more advanced changes. A large number of petechial hæmorrhages were disseminated throughout the white matter of both hemispheres, and there was venous congestion.

Histologically the older child had the less severe cerebral vascular alteration. There was tremendous dilatation of the perivascular spaces which contained large amounts of serous fluid and a few "Gitter" cells. For the most part the transudate was confined to the Virchow-Robin spaces, occasionally, however, it disrupted the limiting glial membrane to contribute to the disturbance of the parenchyma immediately adjoining the vessels. Here the myelin sheaths and axones were disrupted and the glia showed regressive changes. A few "Gitter" cells were present in these areas.

There was an overwhelming predilection of the pathological process for the medium and small veins of the white matter. Significantly the remainder of the vascular apparatus was normal, except for some dilatation and engorgement.

In the younger child the process had progressed to the stage of vasoparalysis and perivascular hæmorrhage. Extremely congested small veins were surrounded by a wide ring of extravasated blood. Most of the smaller blood-vessels, and particularly venules and capillaries in the white substance, were also greatly distended.

These vessels showed the signs considered to be those typical of vasoparalysis Scheinker, 1944*c*): maximal distension and stasis, and degenerative changes or complete necrosis of vessel wall with leakage of blood. The larger extravasations had broken through the limiting glial membrane and had disorganized adjacent nervous parenchyma. These changes were predominant in the white matter. No changes besides congestion were found in larger blood-vessels.

In both cases profound dilatation of venules was associated with transudation of serous fluid and disruption of the adjoining parenchyma of the nervous system. If, as in the younger child, the process went on to the stage of disintegration of the walls of the small veins, presumably a concomitant of hypoxia, perivenous hæmorrhage occurred.

The latter is possibly the precursor of massive cerebral hæmorrhage about which more will be said in the next part. Extravasation of blood is eminently more disorganizing to the parenchyma than is serous transudation. In either case alteration of large vessels is not a prerequisite.

A case summary will illustrate the phenomenon of vasoparalysis in an adult.

A woman (Case 103195) aged 24, previously normal except for dysmenorrhœa, had successive strokes over a period of seventy-four days, which were aptly termed "creeping paralysis" by her family physician. The only visceral signs were a prolongedly fast pulse and mild electrocardiographic change. Generalized petechiæ observed on gross examination of the brain were revealed on microscopic investigation to be maximal dilatation and congestion, and possibly the earliest stage of thrombus formation, due to stagnation in capillaries and veins. Many of these smaller blood-vessels had undergone rather complete necrosis of their walls through which serum and cells had permeated. These changes were considerably more frequent in the grey than in the white matter, and were associated with disseminated and circumscribed areas of softening. Older stages of the process were marked by disseminated areas of glial scar formation. No structural change was present in the larger vessels. We term such cerebral vascular disorder vasoparalysis, or vasothrombosis if softenings typical of vascular occlusion are found in relation to the evidences of functional vascular change.

Comparable changes are seen in the encephalopathy due to arsphenamine (Roseman and Aring, 1941; Scheinker, 1944*a*) which has been ineptly termed hæmorrhagic encephalitis, and in the cerebral reactions to the sulphonamides (Roseman and Aring, 1941; Scheinker, 1943). Trauma to the nervous system may also cause these functional vascular changes,

as may carbon monoxide poisoning or extensive burns of the body, and possibly also heat stroke.

There is little reason to doubt that softening, contiguous to functionally altered small vessels, and even thrombus formation may develop in the brain where large vessels are healthy, and where there is no indication of prior disease in the walls of any of the vessels. Vasoparalysis is associated with extreme dilatation of smaller veins, with stasis and increased permeability, and is therefore a likely precursor of thrombus formation.

Discussion.

In most of the conditions touched on, active functional changes in the vessel wall are envisaged, either spasm and/or relaxation, in response to a number of agents. The degree of harmfulness of such activity appears to depend somewhat on the intensity and the duration of the abnormal stimulus. If there is return of the vessel to normal after a short-lasting spasm it seems possible that nothing more than fleeting symptoms may result, as in the prodromata of migraine, or the neurological symptoms of the cerebral type of carotid sinus syndrome. Prolonged spasm or dilatation might conceivably result in the symptomatology of cerebral softening, the reversibility of the signs depending not only on the duration of abnormal vasomotricity, since the systemic arterial and cerebral venous pressure is of utmost importance in the matter.

There is ample evidence besides that cited to support this concept, particularly in animal experimentation. The paucity of gross occlusion of vessels in the clinical syndrome known as cerebral thrombosis, more properly termed cerebral softening, should arouse suspicion that something more dynamic than mere blocking of a passive vessel is at work. Alternatively, temporary cardiac inefficiency for any reason may result in the delivery of insufficient blood through thickened arterioles, and local softening occur therefore. Cerebral vasomotor change may be combined with cardiac weakness, and the combination result in cerebral damage.

The tendency to blame almost anything and everything on cerebral arteriosclerosis is universal and for this reason, as well as others, is probably a fallacy.

When cerebral arteriosclerosis is not found in the brain of adults reaching our laboratory we wonder why. It is observed much more frequently unassociated with neurological or psychiatric disorder, than with it. It seems safe to say that cerebral arteriosclerosis in our milieu is just about as normal as death.

The term cerebral arteriosclerosis results in ineffective attempts at

therapy. It is probable that every means of cardiac support should be marshalled early in the onset of cerebral softening. Such vasodilators as nicotinic acid and whisky may be used, and oxygen administered judiciously. The vasodilators should most certainly be used in preventive fashion in elderly persons suffering from attacks of vertigo, weakness, and bradycardia.

It may be gathered that we are loath to concede to arteriosclerosis operating as a sole factor, the ability to produce a parenchymal lesion of the type commonly regarded as a stroke. It is too easily forgotten that strokes may occur in infants and children, of whom parenthetically it might be stated that the incidence of vascular death is not known, since these reactions are usually masked under the title "encephalitis" which is just as vague as that of cerebral arteriosclerosis.

We have too long refrained from attributing to reactions that occur in blood-vessels the importance they deserve in the genesis of nervous lesions. Our group is respectful of cerebral vasospasm, vasodilatation, and vasoparalysis, as happenings in sequence which may lead to permanent parenchymal change, and we are aware that the brain is secondary to the heart in circulatory health or circulatory abnormality.

PART II.

THE previous discussion was concerned particularly with certain functional cerebrovascular reactions which may lead to clinical syndromes, detailed variously but with points in common. Among those considered were the prodromata of migraine, the cerebral type of the hypersensitive carotid sinus, cerebral thrombosis and embolism, the brain disease associated with arterial hypertension, and cerebral thrombo-angiitis obliterans.

Finally a condition termed vasoparalysis was presented, a functional disorder of venules and capillaries allowing escape of the vessel content and disruption of parenchyma. It was indicated that vasoparalysis may be associated with a seemingly unlimited number of noxa including trauma to the nervous system, the ingestion of sulphonamides, the intravenous use of arsenicals, poisoning by carbon monoxide, and with extensive body burns; or it may occur in infants or young adults, the latter without previous cerebral vascular disease. Vasoparalysis may be implicated also in the development of the usual types of stroke.

The thought was expressed that cerebral arteriosclerosis *per se* has long enough served the specialist in nervous or mental disease as a faithless crutch. We noted our hesitation to attribute to cerebral arteriosclerosis

alone any clinical syndrome which has been well defined. That it may contribute its quota to that of functional cerebral vascular disorder and cardiac disorder is not doubted.

The importance of the systemic circulation and particularly the heart in the origin of cerebral softening and hæmorrhage (Fleming and Naffziger, 1927) has not been stressed enough. Softening must result often enough in cases where the heart for any reason suddenly becomes transiently inefficient. In a respectable number of cases, a cerebral lesion has been diagnosed clinically when myocardial insufficiency has been operating. This at once suggests one line of approach to the therapy of certain types of apoplexy.

Cerebral Hæmorrhage.

In the previous section it was indicated that despite careful search it was practically impossible to find a gross break in the vessels of persons suffering from intracerebral hæmorrhage. This does not apply to aneurysm at the base, where the bleeding may dissect into the brain rather directly from a leaking vessel. However, in our experience aneurysms do not arise intracerebrally.

It has been thought that symmetrical lesions placed bilaterally in the nervous system may be evidence that a wave or waves of dysfunction may sweep along large vessels. We are not particularly impressed with the idea, but an illustration of the happening is furnished by a woman (Case 137542), aged 70, who survived a mild cerebral hæmorrhage for three years and in whom autopsy revealed symmetrical old lesions in the thalami of the two sides. Another instance of multiple petechial hæmorrhage is that of a 32 year old man (Case 139475) to whom the administration of 112 grams of sulphamethylthiazole over four and a half days was finally associated with cerebral signs (Roseman and Aring, 1941). Remarkably symmetrical, confluent, petechial hæmorrhages were found scattered through the grey matter of the cortex and nuclear masses of the brain-stem. The larger blood-vessel walls were free of structural change.

There is more substantial evidence than this, that cerebral hæmorrhage like cerebral softening may have in its development a functional vascular aspect: and in this respect these clinical conditions are basically similar. Their particular point of divergence is possibly the implication of leaking veins in hæmorrhage. Our studies have led us to the conclusion that cerebral hæmorrhage arises essentially from veins (Cobb and Hubbard, 1929) and not from arteries.

Hypertensive brain disease associated with hæmorrhage.—In marshal-

ling the evidence, let us consider again the histopathology of hypertensive brain disease, possibly the most frequent precursor of cerebral hæmorrhage. A classical case may serve as an epitome.

A coloured woman (Case 5610) was closely followed in our clinic for four years before her death from hypertensive encephalopathy and cardiovascular disease at the age of 45. Her hypertension was found incidentally at the age of 24 when she underwent a gynæcological operation at the Cincinnati General Hospital. In the final four years of life the blood-pressure was usually around 250/150.

Over the last four years of life she was practically an invalid, having repeated strokes; if they were accompanied by weakness it was of hemiplegic or monoplegic distribution. The final episode five months before death was accompanied by vomiting which had been occurring infrequently before, and by the accentuation of right hemiparesis to hemiplegia. She had ten cerebrospinal fluid examinations during four years of observation; half of these, including two done at the time of onset of the final episode, contained liberal amounts of red blood cells.

Grossly this nervous system presented lesions in many stages of development. There were scattered old areas of softening, and a more recent massive hæmorrhage in one occipital lobe. Three fresh ball hæmorrhages were found, one in the white matter of the cerebellum, one in an uncinate gyrus, and one in a frontal lobe.

Histopathological studies.—Microscopically the subarachnoid space was slightly distended and harboured a small number of "Gitter" cells and red blood cells: in some areas dense focal infiltration of the leptomeninges with "Gitter" cells had occurred which communicated with small areas of softening localized in the upper layers of the cortical ribbon.

Besides cerebral arteriosclerosis, there were predominant alterations in small arterioles and veins. The arterioles exhibited findings typical of hypertensive arteriolopathy; conspicuous thickening and hyalinization of the entire vessel wall was associated with a perivascular fibrosis. There was considerable narrowing of the vessel lumen; not rarely it was reduced to a mere slit.

Changes of the nervous tissue secondary to these arteriolar alterations were disseminated throughout the cortical ribbon and the subcortical white matter, and consisted of circumscribed focal areas of softening containing large numbers of fat granule cells, and numerous areas of old softening in the stage of glial scar formation. An occasional lesion of similar character was seen in the pons and cerebellum.

There were striking alterations of the small veins, which exhibited conspicuous atrophy: a thinning of vessel wall. It was by no means rare that the entire wall of a medium-sized vein consisted of only a very thin membrane outlined by a few endothelial cells. In these vessels the normal structure of the muscularis and adventitia could not be recognized.

In addition to the atrophic change some veins were tremendously distended and engorged with blood, and there were signs of increased permeability of the wall for red blood cells since the latter were often seen in large accumulations in the perivascular spaces.

In occasional veins with an extremely advanced stage of congestion the wall had undergone partial or complete necrosis and was surrounded by large extravasations of red blood cells, coalescence of which formed the massive hæmorrhage in the occipital lobe. The central portion of the hæmorrhage had completely destroyed the nervous tissue, and at the periphery there were to be seen a few extremely congested veins with extravasation, forming characteristic ball hæmorrhages.

In addition to the two types of recent hæmorrhage (ball and massive) there were numerous, circumscribed areas of old or "healed" hæmorrhage, containing a dense accumulation of amorphous blood pigment, enclosed in Gitter cells or freely distributed in the nervous tissue. There was heavy gliosis in and about these foci of old hæmorrhage.

Œdema was found in sections taken from the central portions of the white matter where the tissue showed the characteristic spongy, sieve-like appearance, amœboid degeneration and clasmatodendrosis of the glia, and congestion of the veins and capillaries.

In histopathological studies of cerebral hæmorrhage, we have paid particular attention to small discrete hæmorrhage (ball hæmorrhage), and to the areas contiguous to massive hæmorrhage. One is, of course, aware of the fact that the experimental injection of blood into the parenchyma of the central nervous system of animals is attended by small satellite accretions of blood in the neighbourhood of the clot. The blood either insinuates itself along perivascular spaces, occasionally breaking forth and accumulating, or, more likely, its injection induces widespread reaction in the vascular system of the cerebral hemisphere.

With the profound changes in the venules and capillaries associated with hypertensive brain disease in mind, let us go on to a few clinical points of evidence.

Clinical studies.—Signs of progression of the lesion are not uncommon in cerebral hæmorrhage after initial symptoms have announced the onset of bleeding. An excellent history is necessary to determine that symptoms indicating progression may be spread over a period of days before the development of hemiplegia or other catastrophic signs (Aring and Merritt, 1935). This progression of symptoms and signs which occurs with considerably more frequency in cerebral hæmorrhage than in cerebral softening, is frequently confused with premonitory symptomatology which is transitory and possibly concerned with cardiac dysfunction. Progressing signs may be explained by an accumulating lesion such as coalescing perivenular hæmorrhage.

Venous origin of retinal hæmorrhage has been commented upon by Ballantyne (1943) who noted that with change in calibre of veins the circulation becomes slower, the vein wall proximal to the relative obstruction suffering from hypoxia and becoming devitalized thereby. Hæmorrhage through weakened venular walls would then appear to be a matter of time, particularly in the presence of arterial hypertension and/or increased venous pressure.

When large veins within and without the brain parenchyma are involved in a disease process there is no doubt that massive cerebral

hæmorrhage may follow. Such a sequence of events may be seen in patients with venous obstruction associated with mediastinal obliteration. In these cases the venous drainage of the brain is directly and rather gradually interfered with. The microscopic study indicated that a tremendous degree of venous congestion and stasis had occurred followed by coalescence of small, perivenous hæmorrhage.

Experimental studies.—It will be recalled that Villaret and Cachera (1939) recorded photographically the development of cerebral hæmorrhage in the living dog after the production of solid cerebral emboli. They were not able to produce hæmorrhage with air embolization, which in contradistinction to solid embolus produced no vasomotor reaction. Therefore a primary requisite for the production of hæmorrhage in their experiments was not complete obstruction of vessels, but severely disturbed vasomotricity.

This experimental work contains the additional evidence relative to this discussion. All types of hæmorrhagic lesions were encountered: petechial, hæmorrhagic infarction, gross parenchymal and ventricular bleeding. Their microscopic studies revealed some of the characteristic small vessel changes which we have found in human cerebral hæmorrhage; extreme congestion of these vessels was noted as was confluent perivascular hæmorrhage.

Discussion on cerebral hæmorrhage.—It appears that hypertensive brain disease may be associated with abnormalities of vasomotor control, and finally with the attenuation of small and medium sized veins. This attenuation of venules in long-standing hypertension, particularly in cases that have suffered cerebral symptomatology, possibly represents the difference between the occurrence of hæmorrhage and thrombosis in a given case. Cerebral hæmorrhage may occur without venular atrophy, but when it does it appears that the noxa must be rather overwhelming in nature.

In the problem of the origin of cerebral hæmorrhage it would seem that less imagination is required to defend the position holding for leakage from veins rather than from arteries, whether these vessels be normal or diseased. The vein is a relatively delicate structure which does not have a well-developed elastic membrane, and is not designed to accommodate such stress and strain as is the artery, or to compensate for structural disorder. Hypertensive disease appears to thicken the arterioles; in a manner they are reinforced to meet the added tension; simultaneously the venules are enfeebled.

Thin-walled veins offer a small margin of safety from their contained blood, particularly in the presence of abnormal vasomotor reaction.

The arterioles bear the brunt of hyperpiesis, and when this system finally "decompensates", presumably by a process akin to vasoparalysis, abnormal tension may be transmitted from the failing arteriole to the enfeebled vein, the structure next in sequence, which thereafter is likely to loose blood and to cause death. The latter would be especially prone to occur with the attenuated vein of long-standing hypertensive brain disease, where the cause of death is usually cerebral hæmorrhage, unless failure of the kidney has occurred previously.

In the experimental production of vasomotor changes Villaret and Cachera (1929) frequently observed arterial blood in the veins. It might be presumed that a modicum of the arterial pressure may be transmitted across the capillary with the arterial blood.

Our studies suggest that cerebral veins in man respond to functional change in arterioles as they do in the animal. If this is so, reduced blood flow in them, or stasis, may reduce nourishment to the walls of the venules, which has been shown by Landis (1928) to allow sequential loss of the constituents of blood to the surrounding tissue. One may expect the venous pressure to be increased in hypertensive encephalopathy which would also favour disruption of weakened venular walls.

If it were arterial deterioration alone that was responsible for cerebral hæmorrhage one would expect to find the age-incidence at the very least equal to, if not greater than, that of persons suffering from the syndrome of cerebral softening. Anyone who has dealt with a large vascular material clinically knows the rough rule that if a stroke occurs below the age of 50 it is considerably more likely to be hæmorrhage than thrombosis (excluding persons afflicted with meningovascular syphilis, embolism, and the rarer conditions associated with thrombus formation, such as cerebral thrombo-angiitis obliterans).

Another point in favour of venous bleeding is the relatively more haphazard localization of the hæmorrhage than seems to be the case in cerebral softening. In the latter the pattern of softening may follow the distribution of an artery. If it were an artery that had ruptured and then clotted, one would expect secondary softening in the tissues supplied by it, if the patient survived the ictus for the short period of time that would allow softening to occur. Such is not the case in cerebral hæmorrhage.

On clinical, pathological, and experimental grounds we favour the concept of Ricker (1919) and Schwartz (1930) that functional vascular dis-

orders occurs prior to massive hæmorrhage. We would add to their concept that the bleeding is of venous origin.

Circulatory Factor in Spinal Cord Disease.

Some of the conditions already considered may affect the spinal cord as they do the brain. Other disorders wreak damage particularly to the cord, in some instances via certain functional changes in the circulation.

Let us consider briefly the spinal cord disease of anæmia and of extradural compression. Early or late one cannot differentiate the histopathological findings in the cord of these two conditions. In a beginning lesion in either, there are circumscribed areas of axonal swelling and vacuolar degeneration of white matter without glial repair. Later the vacuolar degeneration is widespread in the white matter and unless the disease process is reversed by treatment, there is no attempt at repair. Nerve cells are occasionally damaged.

In subacute combined degeneration the quality of blood is reduced, in extradural compression there is reduction in the quantity. Whether or not functional vascular changes be concerned in the production of these lesions one is unable to say. We have seen no evidence of it.

With restoration of the normal circulation an attempt at repair of the spinal cord occurs, characterized by a dense accumulation of glial fibrils, the interstitial cells being small astrocytes. Close study with appropriate silver stains leads one to think that extremely thin axonic fibrils may possibly be found in the scar.

Clinically we know how very long it may require for restoration of function to occur after extradural compression or in subacute combined degeneration. This has been remarked upon particularly by neurosurgeons after the drainage of extradural spinal abscess. In our last case (Aring, 1944) absolutely no movement occurred in the lower extremities until six weeks after drainage, yet fourteen months later the patient was walking normally, though still using a cane. One has sometimes noted the same slow progress with treatment of anæmic cord disease.

It seems likely that the circulation to the cord in these conditions is not so deficient as to induce complete tissue death within the period of the disease. The extremely slow restitution of function with the restoration of the blood may parallel the glial and the questionable axonal repair, and be dependent on it. It is pertinent to recall that recovering cord function may be inhibited or abolished by intercurrent infection. We have not seen indications of disturbed vasomotricity in this static histo-

pathological picture. Apparently, therefore, reduction of the quality of the blood, or of its amount by slow compression are the mechanisms at work.

Vasoparalysis induced by trauma (Scheinker, 1944c) to vertebræ and contusion of the dura of the spinal cord may mimic the histopathological picture of early anæmic cord disease and of cord compression by extradural tumour, with the addition of the visible functional disturbance of vessels.

The case may be cited (Case 181960) of a boy, aged 9, in whom a bullet fractured the 2nd dorsal vertebra and lacerated the outer layer of the dura at this level, and who died because of bronchopneumonia and pulmonary œdema fifty hours after the injury.

As far as the mid-cervical and mid-thoracic segments of the spinal cord, there could be seen vacuolar degeneration of myelin and irregular swelling of axones, accompanied by dilatation of the smaller veins and capillaries with disorganization of their walls and increased permeability for fluid and cells. The latter signs are typically those of vasoparalysis. It should be noted how nearly the parenchymal changes resemble those of early subacute combined degeneration or of compression of the cord by extradural mass.

By inference only it appears that deprivation of blood supply is operating to some extent in all of these conditions.

Circulatory Factor in Peripheral Nerve Disease.

As an example of the involvement of the peripheral nervous system by vascular reaction one may consider the palsy of Jamaica ginger (Jake paralysis) (Aring, 1942). Practically all examples of this disorder occurred in early 1930 during the prohibition era, when some of this material which had been used as a beverage became contaminated with triorthocresyl phosphate. This alkyl derivative of phenol has the same pharmacological action as carbolic acid. When taken internally it results in widespread capillary injury which the patient does not usually survive. Externally it penetrates the skin to deeper tissues where again it affects blood-vessels, extensive gangrene resulting.

In the small doses that were taken with the ginger extract, it induced a polyneuritis, and as would be expected it was secondary to vascular involvement. The smaller vessels supplying muscles and nerves became involved in a hyperplastic fibrosis which narrowed the lumina considerably. All coats were affected in the hyperplasia and thickening. The larger

vessels were normal. The neuritic signs developed seven to fourteen days after drinking the ginger extract, and have been irreversible in many cases.

Parenthetically it might be mentioned that the gastroenteric tract and other viscera were affected. Death was extremely rarely due directly to the poison, though in 61 per cent. of cases it was attributable to arteriolar disease.

Inexplicable was the system degeneration with glial replacement of the pyramidal tract and tract of Goll, and the nerve cell damage in the anterior horns, since practically never did the vascular reaction involve the central nervous system (in one man, aged 35, there was thrombosis of capillaries in the commissure of the spinal cord). The administration of phosphorous acid esters of the phenols to animals also results in degeneration of long tracts and nerve cells.

Jamaica ginger palsy may offer some hints of the mechanism underlying the development of multiple peripheral neuritis.

Surgical Implications.

The discussion of a few of the relationships between vascular reactions in the nervous system and surgery may be appropriate.

Injury to the nervous system.—Evans and Scheinker (1944) and Scheinker (1944*c*) have published studies on the vascular reactions in trauma. They feel that some of the pernicious effects of brain and cord injury are delivered by means of vasoparalysis.

One knows as yet of no method to correct the hypoxia in, and falling osmotic pressure due to protein loss from, the small vessels in the site affected by vasoparalysis. The rising osmotic pressure in the parenchyma induced by escape of protein perivascularly constitutes a considerable threat since local cerebral œdema probably rapidly follows. It would seem useless as far as the local lesion is concerned to administer plasma and oxygen if these materials could not reach the site until the vasoparalysis was relieved. Since alkalosis, hydration, and inflammation increase permeability they are to be avoided in lesions associated with the latter.

How rapidly the cerebral vessels react to direct trauma is probably best known by the neurosurgeon, who, if he has not handled the brain "mit verstand", or even if he has, sometimes finds himself embarrassed by an organ increasing rapidly in size as a result of acute brain œdema or swelling with or without petechial hæmorrhage. He may then be unable to reconfine the brain to the cranium.

The cases described by Wolf and Sirus (1937) are relative to this part of the discussion. Their cases had operations upon the nervous system in a sitting position and these were followed by the development of multiple cortical hæmorrhagic softenings without occlusion of vessels. In three cases the middle meningeal artery had been severed prior to section of the trigeminal nerve. In the other the upper four cervical nerves on one side were severed.

Though hypotension was a factor in their cases, it seems likely that arterial reactions incident to trauma of arteries close to the nervous system may have been propagated and distant effects obtained, as in the experiments of Villaret and Cachera (1939) with solid cerebral embolism. The latter found persistent (weeks) vasomotor reactions distant from the traumatized artery in which a solid embolus had lodged.

One has seen widespread vasoparalysis in the cerebrum and cerebellum accompanying hæmatomyelia located high in the cervical cord and in the medulla (Case 194598). Presumably the vascular reactions following on hæmatomyelia may be regarded as analogous to those of cerebral trauma, and as in that condition they may be propagated widely in the central nervous system.

The relief of massive cerebral hæmorrhage.—We feel that the only method of rehabilitating the patient with a confined intracerebral hæmorrhage is to evacuate it, and accordingly that practically every massive cerebral hæmorrhage above an undefined size is fatal unless relieved by surgery. The *sine qua non* for successful surgical attack is that blood may not have reached the cerebrospinal fluid spaces, or if it has, in only small amounts. The selection of cases for operation constitutes an extremely delicate diagnostic problem. It helps to have had a relatively wide experience with cerebrovascular disease, and to know the essential differential points between hæmorrhage and softening (Aring and Merritt, 1935). An expertly handled cerebrospinal fluid is of inestimable aid in the evaluation.

It goes without saying that the patient must be got early, before failing vital signs indicate the imminence of death. Such signs may occur, of course, within a few minutes of massive cerebral hæmorrhage, but in those instances the blood has most surely reached the ventricular system and the prognosis is hopeless.

The relief of spinal cord compression.—My final surgical point relative to these studies is that extradural compression, or for that matter any compression of the spinal cord, is to be relieved as quickly as feasible. The

reasons are obvious in the light of what has been said of the marked structural change in the spinal cord with circulatory insufficiency.

Infection reduces spinal function which has already been interfered with, whether via the circulation or not is not known.

Summary.

There can be little doubt that the vasomotor changes in the cerebrum of man may be associated with symptoms. The prodromata of migraine and the neurological symptoms associated with the cerebral type of hypersensitive carotid sinus have been analysed and reasonably may be attributed to local vasospasm within a cerebral hemisphere. In fact, permanent hemiplegia has been recorded after stimulation of the carotid sinus, and various types of neurological deficit after migraine.

The beautiful experiments of Villaret and Cachera with cerebral embolism in the dog have visually demonstrated the sequential formation of both cerebral softening and cerebral hæmorrhage. Cerebral hæmorrhage, to occur with previously normal vessels, appears to have as one requisite cerebral vasomotor change. In the experimental situation, as in man, hæmorrhage arises essentially from venules and becomes massive by coalescence.

Chemical changes may induce vasomotor activity as well as alteration in the permeability of vessels, which possibly may be analogous to the disruption of the protective barriers. Landis demonstrated with oxygen lack the increased permeability of the vessel wall first to fluid then to protein; other mechanisms which act similarly are alkalosis, hydration, and inflammatory change.

Any factor tending toward increased permeability in the face of prior disorders of the cerebral vascular tree presumably may be deleterious. Indeed from a pathological viewpoint increased permeability may be fatal to infants whose vessels were previously normal. In this age-group the disruption of protective barriers of the central nervous system by unknown agents may be synonymous with the phenomenon of vasoparalysis.

It is evident that many neurological disorders may manifest themselves by reason of circulatory deficiency. The state of the cerebral and extracerebral circulation should be allowed an intense moment of cool but imaginative attention in every case of neurological disease before venturing to absolve it, or before suspending judgment on its responsibility. The problem should have this attention whether or not the disorder is among those which have been considered to be primarily vascular; trauma, neo-

plasm, toxin, infection, and diseases of unknown nature may wreak their damage via the blood-vessels.

Since the physiological control of cerebral circulation is largely extracerebral, it logically follows that the blow which finally unbalances this marvellously steady mechanism must usually originate extracerebrally.

We believe many of the manifestations of the well known syndrome of apoplexy, including some but not all of the manifestations of embolism, to be on the basis of dynamic changes occurring in vessels, and/or disorder of cardiovascular mechanisms. The active vascular changes in some cases have no correlation with previous disease of the cerebral vessels; though for cardiac weakness or peripheral circulatory disorder to induce cerebral softening usually requires prior disease of cerebral vessels.

What is known clinically as cerebral thrombosis would better be termed cerebral softening, since it has been associated with vasoparalytic phenomena with significant frequency in our experience, and thrombus formation has not been demonstrable; or it has occurred with diseased vessels in the event of cardiac weakness, again without demonstrable thrombus formation.

In our clinical and pathological interpretations cerebral hæmorrhage is associated with perivenous diapedesis with conglomeration.

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TRAUMATIC INJURIES OF PERIPHERAL NERVES.

I.—SIMPLE COMPRESSION INJURIES OF THE RADIAL NERVE.

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THE observations described in this communication were made with the object of determining the course of regeneration in simple compression lesions of the radial nerve.

Disturbances of conduction arising as the result of the application of pressure to a nerve trunk have frequently been the subject of study and comment (Bastien and Vulpian (1855), Waller (1862), Wier Mitchell (1872), Erb (1876), Lüderitz (1881), Zederbaum (1883), Efron (1885), Herzen (1886), Goldscheider (1886), Dejerine and Bernheim (1899), Calugareanu (1901), Ducceschi (1901), Bethe (1903), Semenoff (1903), Meak and Leaper (1910), Fabritius and Bermann (1913), Stopford (1916), Edwards and Cattell (1928), Reid (1928), Gasser and Erlanger (1929), Lewis, Pickering and Rothschild (1931), Clark, Hughes and Gasser, (1935), Grundfest (1936), Thompson and Kimball (1936), Lewis and Pochin (1938), Bentley and Schlapp (1943), Weiss and Davis (1943), Denny-Brown and Brenner (1944 *a*, *b*)). Compression injuries of the radial nerve which comprise principally the "sleep" and "crutch" palsies have, however, rarely been the object of special investigation and a search of the literature has failed to reveal any information concerning the time of appearance, order, rate or time of completion of regeneration following such injuries despite the fact that they have long been familiar to the clinician. These details have been recorded following anatomical interruption of the nerve fibres but they are also desirable in those cases in which there is an interruption of conductivity without loss of fibre continuity. Only when these details are available is it possible to determine whether the course of regeneration varies in the two types of lesion, whether there are any distinguishing or selective features associated with the regenerative process when the lesion does not involve actual severance of the nerve fibres, and whether any similarity exists between the clinical findings and those provided by experimental investigations.

The number of patients examined with the above objects in view is admittedly small but, since opportunities for conducting such investiga-

tions and for pursuing them to completion are infrequent, it is believed that the results obtained are worth reporting.

Literature.

Most investigations into the effects of nerve compression have been experimental in character and have been concerned principally with problems which have only an indirect, if any, bearing on the clinical features presented by this type of lesion. A detailed review of these researches is consequently not called for and reference will be made only to those observations which are relevant to the subject under consideration.

In 1862 Waller described the effects of compressing the radial nerve in his own arm. Thirty minutes after the application of the pressure the skin on the back of the hand was "somewhat insensible" and the wrist extensors were paralysed. At the end of forty-five minutes all muscles innervated by the radial nerve were paralysed and the involved cutaneous areas, which from his description corresponded to those of the dorsal cutaneous nerve of the forearm and superficial radial nerve, were "nearly insensible to contact" but "when pricked or pinched pain was produced of a hot burning character which lasted for about a minute after the removal of the cause." The pressure was then released. Recovery of motor and sensory functions commenced simultaneously and steadily improved until, after a lapse of twelve days, function was normal in every respect. Similar experiments were carried out on the median and ulnar nerves. In the case of the latter, signs of disturbed sensation preceded the onset of weakness which first appeared in the interossei though no times were given. In the median nerve, paralysis and numbness were observed at the end of thirty minutes though there is no note as to whether or not they appeared simultaneously. In both nerves the events subsequent to the release of the pressure were not described.

Erb in 1876 directed attention to a type of peripheral nerve lesion, due to localized pressure, in which motor function was lost while the electrical excitability of the involved muscles remained unaltered. This he referred to as the intermediate form of reaction of degeneration. The preservation of electrical excitability in the presence of paralysis was also observed by Dejerine and Bernheim (1899) in a case of sleep palsy which came to autopsy twenty-five days later when the significant observation was made that Wallerian degeneration was present only in the nerve to brachioradialis.

Working on the sciatic nerve in the rabbit, Lüderitz (1881) first demonstrated experimentally that motor fibres are more susceptible to compression

than sensory fibres and though Zederbaum (1883), Efron (1885) and Ducceschi (1901) failed to confirm this observation more recent researches indicate that it is essentially correct.

A syndrome of compression, arising as a result of scar tissue contraction following gunshot injuries of peripheral nerves, has been described by Stopford (1916). The first signs of compression were loss of conduction in the motor fibres and severe pain which were succeeded by analgesia and later by tactile anæsthesia which was never so extensive as the analgesia. The nature of the injuries and the conditions obtaining in his cases were such, however, as to exclude them from the group here described as simple compression injuries.

The behaviour of limb muscles and nerves during experimental ischæmia has been investigated by Reid (1928) and Lewis, Pickering and Rothschild (1931). Reid observed that under these conditions in man muscle contraction fails in about twenty-five to thirty minutes but is fully restored ten to twelve minutes after the re-establishment of the circulation. During the period of paralysis contractile responses could still be obtained by stimulation of the nerve trunk below the point of interruption of conduction. He believed the effect of ischæmia to be a selective one "on the field of conjunction between nerve and muscle."

In Lewis, Pickering and Rothschild's experiments numbness appeared thirteen to fifteen minutes after the obstruction of blood flow and was rapidly followed by anæsthesia and impairment of cold perception. Though the pain sense changed in quality there was no absolute analgesia after a lapse of forty minutes. Paralysis of voluntary movement was established "between the 25th to 29th minutes of arrested blood flow." The disturbances developed in an order which was, in general, centripetal. With the readmission of the blood to the limb following an obstruction of twenty-five to thirty-five minutes sensation returned to normal in about twenty-five to fifty seconds. The recovery of muscular power was well advanced in seven minutes but did not completely recover for a further ten minutes. After long circulatory arrest (thirty-five to forty minutes) the nerves took some hours to recover fully. These authors carried their investigations a stage further and established a distinction between this type of paralysis and that resulting when the pressure is confined to a short segment of a nerve trunk. The differences reported by them involve principally the mode of onset and progression of the motor and sensory changes and were attributed to the different methods employed for producing the pressure block. Thus, after the direct application of pressure to the ulnar nerve at the medial epicondyle of the humerus, anæsthesia and muscular palsy

were not established until thirty to forty minutes had elapsed. Anæsthesia and impairment of cold perception developed simultaneously but absolute analgesia was not present at the end of ninety minutes. When the pressure was released thirty minutes later recovery occurred in much the same time period as in the cuff compression experiment. The effects in both sets of experiments were attributed to the devascularization of the nerve within the region of pressure while the order of loss of function was explained in terms of the diameter of the fibres—the larger being more susceptible to ischæmia than the smaller.

The results reported by Reid, and by Lewis, Pickering, and Rothschild, differ in some respects from those presented by Waller—notably in the time taken for function to recover fully. The nerve investigated and the method of inducing the paralysis were not the same in each instance, however, and this would probably account for the reported differences.

Characteristic differences between nerve block due to pressure itself and that due to ischæmia have also been demonstrated in acute experiments by Bentley and Schlapp (1943). According to them the development of the former is much slower, and the persistence of the block for some hours after the release of pressure is in marked contrast to the rapid recovery which follows relief of ischæmia.

More recently Weiss and Davis (1943) and Denny-Brown and Brenner (1944*a*, *b*) have studied—the latter in considerable detail—the effects of pressure directly applied to a short segment of a nerve trunk. The former effected a pressure block in the nerve by applying arterial sleeves to the peroneal and tibial nerve in the rat. They claim "that a fibre of morphologically sound appearance may yet be inoperative physiologically" so that "histological continuity of nerve fibres does not necessarily imply passage of impulses." They attribute the actual cause of degeneration, when it occurs, not to ischæmia of the compressed segment but to the arrest of "the centrifugal flow inside the axon of substances or factors vital for the maintenance of axonal integrity."

Denny-Brown and Brenner (1944*a*, *b*) studied the relation of the pressure applied to the sciatic nerve of the cat to the onset and duration of the paralysis and to the associated histological changes in the nerve. The following are the main points which characterized the pressure syndrome as described by them: (1) there was little, if any, impairment of sensation but when the latter was involved the conduction of motor impulses failed before those subserving sensation; (2) the electrical excitability of the nerve and muscle below the lesion were preserved until recovery occurred; (3) the onset of paralysis was, in general, more rapid the greater the pressure

—this they explained on the basis of relative degrees of ischæmia; (4) motor conduction reappeared between the 5th and 19th day and proceeded rapidly to completion; (5) histological changes in the nerve at the site of the pressure were represented by œdema, lymphocytic infiltration, granulation, fissuration and vacuolation of the myelin at the nodes of Ranvier with, finally, exposure of the axis cylinder; (6) providing continuity of the fibre was retained, a stage short of degeneration might obtain for nineteen days by which time recovery of conduction appeared; (7) they found that these histological changes outlasted the return of conductivity and that "restitution of the myelin defect was only slightly advanced after six to eight weeks and was still defective after six months"; (8) in the absence of nerve impulses atrophy of paralysed muscle appeared to be prevented by anatomical connection with the motor neurone. On the basis of their findings they concluded that "compression of mammalian nerve without angulation must be effective through the related ischæmia," a conclusion which is in general agreement with the observations of previous workers (Lewis, Pickering and Rothschild (1931); Clark, Hughes and Gasser (1935); Grundfest (1936): Thompson and Kimball (1936)).

Clinical Material.

Seven cases have been investigated. In five of these the nerve was compressed during sleep, in one it was injured when the arm of the patient was pinned beneath a truck while in the seventh the lesion followed the faulty use of crutches. Observations on the appearance, rate and order of regeneration together with the time required to establish complete restoration of function have been set out in the accompanying table.

Restoration of function was regarded as being complete when all movements were full in range and in power, as measured by dynamometer and spring balance readings, and when sensation was normal and there was no wasting. No attempt was made, in studying the return of function, to separate respectively the two radial extensors of the wrist, the abductor pollicis longus from the extensor pollicis brevis, and the segment of the extensor digitorum communis to the index finger from the extensor indicis proprius. The members of each group have substantially the same actions and are so closely associated anatomically that it is often impossible to decide definitely by palpation when one is contracting and the other is not. Palpable contraction of the muscle, or movement which was undoubtedly attributable to its action alone, were the criteria adopted for detecting returning function and in this connection due regard was paid to the possibility of transmitted contraction and trick movements.

Wasting was estimated by comparing the measurements of the circumference of both limbs 7·5 cm. above and below the medial epicondyle of the humerus.

The patients were examined at three-day intervals until all muscles were contracting from which time onwards the examinations were conducted at weekly intervals.

The treatment in all cases consisted of daily massage, heat therapy, exercises, and controlled splinting. Electrotherapy was not employed.

Personal Cases.

Case 1.—Private T. M., aged 50, retired to bed on a hard straw mattress after celebrating Boxing Night, 1941, with copious quantities of beer. He slept "like a log" all night and the following morning found that his left arm felt weak and useless when he unsuccessfully attempted to fold his blanket. He was unable to provide any information concerning the position in which he had slept or whether his left arm had been compressed during the night. The patient could in no way be regarded as a chronic alcoholic.

On examination twelve days later triceps function was found to be unimpaired. The remaining muscles innervated by the radial nerve were paralysed. All forms of sensation were normal and there was no history of any paræsthesiæ. There was no wasting—probably owing to the fact that recovery commenced before it could make its appearance.

Regeneration first appeared simultaneously in the three extensors of the wrist and in the abductor pollicis longus eighteen days after the onset of the paralysis, and the patient was returned to his unit fifty-six days later with limb function normal in every respect.

Case 2.—On March 14, 1942, Private J. V. G., aged 26, awakened, after sleeping without bedding all night on the deck of a transport, to find that he could not lift his right hand when he reached for his glasses. He had slept soundly through the night within a foot of a steel bulkhead on his right side, but did not recall having struck the arm on any firm object during the night; nor had he, to the best of his knowledge, slept on his arm. No history of alcohol and no loss of weight or undue fatigue.

When first examined by me on April 14, 1942, radial nerve function, both motor and sensory, was absent below the supply to triceps. There was 1·5 cm. of wasting. The patient was last examined on May 14, 1942 (that is sixty-one days after the onset of paralysis) when the condition was unchanged. He was then transferred to an American Army Hospital.

Enquiries in September, 1942, revealed that by August he had completely recovered though no details were available concerning the course of regeneration. It can therefore be concluded that in the interim between 61 days and 5 months regeneration commenced and proceeded to completion.

Case 3.—Private G. A. G., aged 27. Amputation of the right leg, eight inches below the knee and amputation of the toes of the left foot in May, 1942. The patient commenced to use crutches in August and weakness of the right arm was first noticed in October. When examined on October 6, 1942, all muscles supplied by the right radial nerve were severely paresed—no movements could be executed against gravity and only a flicker of movement was possible when this factor was removed. Sensation was normal and there was no history of any paræsthesiæ.

Function was completely restored on January 28, 1943, approximately 120 days after the appearance of weakness. During recovery there was a lag in the return of power to the triceps and brachioradialis muscles.

Case 4.—Private F. A. W., aged 30, awakened on the morning of January 30, 1943, to find that his left hand was powerless. He had slept soundly all night on a hard straw mattress and could in no way connect any unusual event during the night with his disability. No history of alcohol and no loss of weight or fatigue.

On examination ten days later triceps function was found to be unimpaired. The remaining muscles innervated by the radial nerve were paralysed. Sensation was normal and there was no history of any paræsthesiæ.

Recovery was first observed in the extensores carpi radiales seventeen days after the onset of the paralysis and function was restored to normal after the lapse of a further fifty-nine days.

Case 5.—Private F. C. K., aged 33, suffered grenade wounds of the left buttock, thigh and leg on the afternoon of November 6, 1943. Ten minutes after being wounded the patient was given an injection of morphia into the right upper arm, but the site of injection was not related to the radial nerve. The patient was then transported for several hours by stretcher down a mountainside. Next morning he found that his right wrist, fingers and thumb would not function when he attempted to roll a cigarette. The patient was extremely fatigued and below normal weight.

Examination revealed a complete lesion of the right radial nerve below the supply to the triceps while sensation was impaired in the field of the superficial radial nerve. The evidence available suggested that the radial nerve had suffered severe and prolonged pressure against the edge of the stretcher during transit down the mountainside.

The abductor pollicis longus, extensor pollicis longus, extensor communis and extensor carpi ulnaris all commenced to contract 48 days after the onset of paralysis. Motor function was normal 164 days after the injury, but the sensory defect persisted for a further 92 days.

Case 6.—Private K. A. J., aged 31, was involved in an accident on May 7, 1944, in which his right arm was pinned for about one and a half hours beneath the door of an overturned truck. The line of maximal pressure crossed the lateral aspect of the arm in the region of the elbow joint. On examination the brachioradialis was found to be contracting weakly but the muscles supplied by the radial nerve below it were paralysed. Sensation was impaired over the dorsum of the hand. The muscles supplied by the ulnar nerve showed a mild paresis while the cutaneous field of this nerve was hypalgesic.

Ulnar nerve function was restored to normal on July 7. The radial extensors of the wrist commenced to contract 17 days after the injury. The sensory defect persisted for 31 days while complete restoration of motor function was registered 136 days after the injury. Measurements of the right arm always exceeded those on the left, but by the time complete restoration of motor function had been recorded they had improved by 1·1 cm. on the involved side while those on the left had remained constant.

Case 7.—Sailor J. M., aged 30, fell into a sound sleep on a leather cushion on a wooden form. He had previously lost weight and was severely fatigued after a long period of active service at sea. He went to sleep on his right side with his right arm beneath him. On awakening the following morning he thought his right wrist had "gone to sleep"—his hand felt powerless and for a few minutes there was a sensation of "pins and needles" over the dorsum of the right forearm and hand. When examined three hours later all muscles supplied by the radial nerve

SIMPLE COMPRESSION LESIONS OF THE RADIAL NERVE.

Case	Return of voluntary contraction in days						Sensation	Wasting	Time required to re-establish normal function in days
	BR	*E.C.R.*	*E.C.U.*	*E.D.C.*	*A.P.L.*	*E.P.L.*			
1. T. M.	28	18	18	28	18	21	Normal	Absent	74
2. T. V. G.	61–150	61–150	61–150	61–150	61–150	61–150	Defective in the field of the dorsal cutaneous of forearm and superficial radial	Present	61–150
3. G. A. G.	—	—	—	—	—	—	Normal	Present	120
4. F. A. W.	55	17	20–27	20–27	20–27	20–27	Normal	Absent	76
5. F. C. K.	60	53	48	48	48	48	Defective in the field of the superficial radial	Present	Motor : 164 Sensation : 256
6. K. A. J.	—	17	20	31	23	23	Defective in the field of the superficial radial	Present	136
7. J. M.	46	37	35	31	35	35	Transitory paræsthesiæ in the field of the dorsal cutaneous of the forearm and superficial radial nerves	Present	100

The muscles are recorded by means of their initial letters, e.g. BR = Brachioradialis.

below and including the brachioradialis were paralysed, but the most careful tests could elicit no sensory defect. One month after the onset the right arm showed wasting to the extent of 1·5 cm.

Function reappeared in the extensor digitorum communis 31 days after the onset of paralysis and had completely recovered at the end of 100 days.

Observations and Comment.

Motor system.—In the case of "crutch" palsy removal of the causative agent arrested the condition on the verge of paralysis. In the remaining cases the muscles below and including the brachioradialis were paralysed with the exception of Case 6 in whom some branches to the brachioradialis escaped. From this it may be concluded that all the motor fibres had been damaged to the point of interruption of conduction but whether to the same degree or not it is impossible to say. Studies on the order of returning contraction and the time required for the full restoration of power in individual muscles suggest that the degree of involvement of individual fibres does vary and that this is probably determined by such factors as the position of the fibre in the nerve, the relative susceptibility of individual motor fibres and the duration and severity of compression.

Electrical reactions.—The patients were usually investigated under conditions which did not permit the recording of the electrical reactions at regular and critical periods following the onset of paralysis. For this reason information in this respect is lacking in both completeness and detail.

The reactions were not obtained in Cases 3, 4, and 5. In Case 1, the excitability to stimulation was first examined eighteen days after the onset when the abductor pollicis longus and wrist extensors were alone contracting voluntarily. At that time all the muscles responded normally to galvanism and each gave a weak normal reaction to faradism. In Case 2, a reaction of degeneration persisted until the patient was last examined by me. In Case 6, the reactions were first obtained six days after the injury and were normal. Thus in this patient the reactions were normal eleven days before the appearance of voluntary contraction. In Case 7, the reactions were first taken out thirty-five days after the injury. All muscles gave a slow sluggish response to galvanism and a weak normal response to faradism. At this stage all but the extensores carpi radiales and brachioradialis were contracting voluntarily.

The appearance and persistence of a reaction of degeneration in Case 2 is consistent with the distal segment having undergone complete Wallerian degeneration and this is supported by the long interval between the onset of paralysis and the appearance of recovery. Cases 1, 7 and

particularly 6, however, provide evidence which confirms the generally accepted opinion that electrical excitability is retained in the presence of paralysis though it is to be noted that some impairment of excitability does accompany the motor loss.

Sensation.—Disturbances of sensation were uncommon and when present were not a prominent feature of the lesion. A history of paræsthesiæ could be obtained from only one patient (Case 7). In this instance they were, from his description, localized to the fields of the dorsal cutaneous nerve of the forearm and superficial radial nerve and lasted only a few minutes. They could, however, have been present and passed unnoticed owing to the condition of the patient in Cases 1, 5 and 6 but in 2, 3 and 4 conditions were such that, had they been at all marked, they might reasonably have been expected to disturb the patient as they developed.

Sensation was not affected objectively in Case 7 and, though Cases 1 and 4 were not examined by me until twelve to ten days respectively after the injury, there is good reason for believing, from the history, that it was not involved in them.

Objective sensory defects were present in three cases. In one the compression was severe (Case 6) and in another prolonged under the influence of morphia (Case 5). In both, all forms of sensation were impaired in the field of the superficial radial nerve and remained so for 31 days in one case and 256 in the other. In the third patient (Case 2), all forms of sensation were lost in the field of the dorsal cutaneous nerve of the forearm but pinprick was distinctly sharper than normal in the field of the superficial radial nerve. The defect was still present and unchanged 61 days after the onset of the condition—no further record as regards sensory function is available though presumably it returned to normal with complete restoration of function in the motor system.

The general conclusion is that interruption of conduction in such injuries is selective in character, the motor fibres being more susceptible than the sensory, and in this respect these observations are in agreement with those of Erb (1876), Lüderitz (1881), and Denny-Brown and Brenner (1944).

The development of sensory defects appears, in some respects, to be related to the severity of the lesion if one accepts as the criteria of severity the length of time before the reappearance of contraction and the time required for complete restoration of function. This is borne out by a study of the course of events in Cases 2, 5 and 6. The clinical evidence suggests that when sensory defects accompany the lesion and are well established the restoration of full motor function will be delayed longer

than otherwise. The observations made throw no light on the question of differential susceptibility of the fibres subserving the different forms of sensation.

Wasting.—Particular interest attaches to the condition of the limb as regards wasting in view of the statement by Denny-Brown and Brenner (1944) that "anatomic continuity of nerve, not receipt of impulses, prevents atrophy and fibrillation of muscle."

Wasting was estimated by comparing the measurements of the circumference of both limbs 7·5 cm. above and below the medial epicondyle of the humerus. All patients were right-handed—from which it may be reasonably inferred that the dimensions of the right limb should normally be not less than those on the left. Consequently when the measurements on the right were found to be less than those on the left the difference could be definitely attributed to wasting.

There was never any wasting in Cases 1 and 4, probably owing to the fact that recovery commenced too early and advanced too rapidly for it to make an appearance. That the rate at which power is restored is of some significance is suggested by a comparison of the condition of the limb in these cases with that in Case 6. Recovery first appeared in all three at approximately the same time but in Case 6 advanced more slowly and took almost twice as long to proceed to completion. In this case wasting was observed.

The wasting in Case 2 calls for no comment since it is adequately explained by the prolonged period of paralysis.

In the remaining cases wasting was present though it never exceeded 1·5 cm. This is a finding which is in marked contrast with what is customarily seen when the nerve has been severed. In such cases wasting up to 3·5 cm. is frequently recorded. I am unable to say when the wasting first appeared in Cases 5 and 7 but it was well established 87 days and 28 days respectively after the injury.

The wasting observed could be attributed indirectly to disuse or directly to the interruption of conduction or to a combination of these two factors. In this connection the following points are of significance: (1) the distribution of wasting, which direct observation reveals more accurately than measurement, was maximal in the lateral epicondylar muscle mass; (2) wasting occurred and was more marked in the more severe lesions; (3) the treatment and the extent to which all parts of the limb were used during recovery were such that the wasting which persisted could hardly be explained entirely on the basis of disuse; (4) the disappearance of wasting closely paralleled the return to normal power.

Though disuse is undoubtedly responsible for some of the wasting there would appear to be good grounds for concluding that a proportion, how much it is impossible to say on the evidence available, is directly attributable to the nerve injury.

Site of involvement.—In "crutch" palsy the nerve trunk and its branches in the axilla, which descend with it to supply the triceps, are compressed against the sharp tendon of the latissimus dorsi or in the tendinous angle at the axillary outlet outlined by that muscle and the long head of triceps.

In the "sleep" palsies the evidence suggests that the nerve is compressed where, or shortly after, it pierces the lateral intermuscular septum. Here the nerve is relatively superficial and directly applied to bone while the fibres to brachioradialis have not yet branched from the trunk. The dorsal cutaneous nerve of the forearm is less intimately related to bone throughout its course—particularly where it becomes superficial—and this may be one of the factors accounting for its escape. On occasions, however, conditions may be such that this branch is involved. The site of injury requires no explanation in Case 6.

Predisposing factors.—It is frequently stated that it is rare for the nerve of a perfectly healthy individual to suffer injury during sleep and that in the majority of patients the peripheral nerves have already been rendered vulnerable by chronic alcoholism. Debility, chronic plumbism and recent infections such as typhoid are also quoted as predisposing factors.

In Cases 2 and 4, predisposing factors were unquestionably absent. In Case 1, alcohol could be held responsible only in that it rendered the patient less capable of correcting the abnormal position responsible for the lesion. In Cases 5 and 7, loss of weight and extreme fatigue were prominent features, while in 5, the additional factor of induced sleep is of importance. There is, therefore, every reason to believe that a normal nerve can be involved if the compression is sufficiently severe and appropriately applied and maintained with reference to the nerve—particularly if wasting has left the nerve unprotected and/or some factor, such as undue fatigue or drugs, deprives the individual of those protective reactions which normally prevent the development and persistence of those conditions which result in nerve block. Age appears to have no influence as a predisposing factor.

Regeneration.—(1) All cases proceeded spontaneously to complete restoration of function. This is consistent with the nature of the injury and the preservation of the intraneural fibre pattern.

(2) Dynamometer and spring-balance readings of muscle action indicate

that this normal state is not usually reached until approximately three to four months after the onset of paralysis (in two cases of this series, however, the period was prolonged) though the muscles commence to contract long before this time. Such delay may be accounted for by the persistence of histological changes in the nerve.

(3) Certain muscles, notably the brachioradialis, are more prone to severe impairment than others. This cannot be accounted for in terms of the length of the fibres of supply from the site of injury. This observation is of interest as Dejerine and Bernheim (1899) have reported Wallerian degeneration in this branch only. A possible explanation for this may be that the branch to the brachioradialis is more severely involved either because of an exposed position in the nerve trunk at the site of injury or because it is separately and more directly involved after it has left the main trunk.

(4) The first muscles to contract are not necessarily the first to recover completely their power. This lag in restoration of power, as distinct from the time of appearance of recovery, was an outstanding feature in some cases. It can be explained on the basis of varying degrees of involvement of different fibres supplying the same muscle.

A comparison of the information obtained from the present investigation with that derived from the study of sutured nerves reveals several unusual and significant features concerning the regenerative process following on compression injuries.

(1) The spontaneous reappearance of motor conduction occurs after an initial period of delay which varies from fifteen to sixty-one plus days and apparently depends on the severity and duration of the compression.

(2) Recovery appears simultaneously in muscles whose nerve-fibre length from the site of injury differs widely. If there is any difference in the time of reappearance of contraction in muscles it cannot exceed three days which represents the interval between examinations.

(3) There is no orderly progress of regeneration down the nerve with the reinnervation of muscles determined by the site of origin and length of their branches.

(4) Keeping in mind the fact that frequently two or more muscles commence to contract simultaneously, it has been observed that once conduction reappears in one muscle a short interval elapses before all muscles supplied by the nerve are contracting. The one notable exception is the brachioradialis, contraction in which is frequently delayed for periods out of all proportion to the others. This sequence of events is rarely seen following severance and suture of the nerve at a corresponding level.

(5) The site of the first appearance of recovery varies and on occasions more distally-supplied muscles have been observed to recover before those innervated at a higher level.

(6) The time of appearance of motor function and the time taken to recover power completely in the various muscles are in no way related to the length of the fibres of supply from the site of injury. Observed differences in these features can best be accounted for in terms of the severity and duration of the compression, the position of the fibres in the nerve, and the degree of involvement and relative susceptibility of individual fibres.

It is impossible to explain the observations here reported on the basis of customarily-held theories regarding the phenomena of degeneration and regeneration; that is, on the basis that the nerve distal to the site of injury undergoes complete Wallerian degeneration and is then reinnervated by the growth distally or regenerating axons—unless of course the rate of growth greatly exceeds that reported following suture of a nerve, either experimentally or clinically. The accumulated evidence rather supports the belief that the histopathological changes leading to interruption of conduction in simple compression injuries must differ, in some respects at least, from those seen following a breach of continuity of the nerve-fibres. These changes apparently do not involve Wallerian degeneration and are evidently reversible in character. In this connection the recent experimental investigations of Denny-Brown and Brenner on the histological changes in tourniquet and clip-pressure paralysis and of Weiss and Davis on pressure block caused by arterial sleeves are of considerable interest.

Character of the lesion.—The preservation of normal sensation in the presence of well-established paralysis is a striking feature in many of these cases and is in marked contrast to the pressure effects reported by Waller (1862) and Lewis, Pickering and Rothschild (1931). These differences are difficult to reconcile. The histological studies of Denny-Brown and Brenner (1944) provide no explanation of this dissociation. There is proof that sensory fibres react less readily to pressure than motor fibres though the former obviously succumb if the pressure is raised and maintained at a sufficiently high level. The dissociation cannot, however, be explained solely in terms of varying degrees of pressure since in the cases reported in this paper the pressure responsible for the lesion presumably exceeded in degree that employed by Waller and Lewis and his co-workers (taking as a measure of the severity and duration of compression the time required to re-establish normal function) and yet sensation remained unimpaired.

Though the actual size of fibres is apparently without significance

(Denny-Brown and Brenner), their differential susceptibility to pressure must be dependent, in some measure at least, on anatomical factors. Thus the escape of the dosal cutaneous nerve of the forearm can be explained solely on the basis of the separate and protected course normally taken by this branch at the site of compression. The escape of the superficial radial nerve fibres cannot, however, be accounted for in this manner since they are contained within the main trunk at the point where the latter is compressed (personal observations). The individual sensory fibres may, however, owe their protection to the position occupied by them within the trunk and this possibility is being subjected to further investigation.

Again, the resistance of the sensory fibres may be due to some as yet unexplained biochemical or morphological properties which render them less susceptible to pressure and ischæmia. In this connection it is interesting to note that Denny-Brown and Brenner (1944) concluded, on the basis of their observations, that the dissociation is due "to a functional property of the disorder of the axoplasm." If this be the sole explanation, however, how is the early impairment of sensation in the experimental work (Waller, 1862; Lewis, Pickering and Rothschild, 1931) to be accounted for. The evidence at present available rather suggests that the dissociation depends, not on a single factor but on a combination of factors.

Though the investigation here reported was, by virtue of the nature of the material examined, limited to a study of the results of pressure block, as opposed to the elucidation of the factors involved in its production, nevertheless certain possibilities suggest themselves in connection with the latter. Thus the disposition of the sensory fibres in the main trunk, together with their inherent resistance to pressure and ischæmia may be such that, at pressures just sufficient to block motor conduction, they resist involvement. The pressure, however, may reach a level at which these protective mechanisms fail and the sensory fibres then suffer the same fate as the neighbouring motor fibres. If this is so the motor fibres which have already succumbed at lower pressures should become progressively more severely involved as the pressure rises to the level which reaches the sensory fibres. Such an interpretation receives support from the sequence of events observed in Cases 2 and 5 where the presence of sensory signs was associated with an unusually long period before the appearance of voluntary contraction. Additional support is also provided by the experimental studies of Denny-Brown and Brenner (1944) who demonstrated that "after pressure for two hours or less sensation may be impaired, but has recovered in a few hours, and the block is then usually one of motor conduction only, lasting two to eighteen days. Sufficiently intense pressure for two hours produces a more prolonged paralysis of

both sensation and muscular power, lasting six to eight weeks before the first signs of recovery."

On the other hand, the pressure and the disposition of the sensory fibres may be such that their inherent resistance is ineffective at quite low thresholds, in which case sensory defects make their appearance concurrently with impairment of voluntary contraction. Here, however, the motor-fibres would not be involved to the same degree at such low pressures and should, as a result, recover in a shorter interval—that this is so is borne out by a study of the findings observed in Case 6.

Such an interpretation must be regarded as provisional only. It obviously leaves unexplained the fundamental and crucial problem of the inherent and differential susceptibility of nerve fibres to pressure and ischæmia. Purely clinical studies, however, are unlikely to provide a solution to this particular problem which awaits further and more intensive experimental investigation.

Summary.

The effects of, and the course of regeneration in, simple compression injuries of the radial nerve (sleep, crutch and traumatic) have been investigated in seven cases. With certain exceptions all the motor-fibres were damaged to the point of interruption of conduction. There was a variation in degree of involvement and the factors responsible for this have been discussed.

A striking feature in many cases of well-established paralysis is the preservation of normal or slightly impaired electrical excitability and of normal sensation in the field of the involved nerve. The significance of this dissociation has been discussed.

The evidence suggests that sensory defects appear in the more severe injuries and that when they are well established restoration of full motor function will be considerably delayed.

Wasting directly attributable to the nerve block was observed in five cases. Its absence in the other two is explained.

It has been established that a normal nerve may be involved during sleep if the compression is sufficiently severe and prolonged—particularly if wasting has left the nerve unprotected and/or some factor, such as undue fatigue or drugs, deprives the individual of those protective reactions which normally prevent the development and persistence of those conditions which result in nerve block.

All cases proceeded spontaneously to complete restoration of function. In five cases this state was reached three to four months after the injury but in the remaining two cases this period was prolonged.

The course of regeneration differed in several respects from that

observed when the fibres have been severed. These have been discussed.

The course of regeneration observed in these cases supports the belief that the histopathological changes leading to interruption of conduction in simple compression injuries must differ from those occurring after anatomical interruption of the nerve fibres. These changes are reversible and apparently do not involve Wallerian degeneration. Such an interpretation is supported by recent experimental work which is discussed in relationship to the clinical observations made in this investigation.

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Notices of Recent Publications.

Acute Injuries of the Head. By G. F. Rowbotham. Second Edition. Livingstone, Edinburgh. 1945. Pp. 414. Price 30s.

The early appearance of this second and enlarged edition is the mark of the great and deserved success this book has achieved since its first publication in 1942. The major importance of the traumatic surgery of the skull and brain was beginning to be realized by neurosurgeons even before the war, and neurosurgery was shaking loose from its too exclusive preoccupation with the grim problems of intracranial tumour, problems which, although they afforded admirable opportunities for the exercise of skill and the development of instruments and techniques too seldom yielded therapeutic fruits of encouraging quality. Nevertheless those years of trial and experience have not been wasted, and neurosurgeons now approach the problems of head injury with their far more widespread importance and encouraging prognosis, with an equipment of theoretical and practical knowledge that has been of immense value, and has saved numberless lives and averted much suffering and disability during the present war. No branch of surgery has more distinguished itself in the past five years, and there could be no better exposition of it than Mr. Rowbotham has provided. It is likely to become the standard work on its subject.

While much of his book deals with the practical problems of the surgeon, the chapters dealing with the clinical aspect of head injuries are of the first importance to the neurologist. Signs and symptoms and their combinations, and the course of cases of head injury of all types and grades of severity, are recorded and described with a precision and comprehensiveness in accord with the best traditions of clinical neurology. In all aspects of his subject the author gives evidence of mature judgment, of a fine clinical sense and of a profound insight into the human problem of handling patients at all stages of their illness. As is always true of genuine psychological insight, this owes nothing to familiarity with current psychological teachings or to adherence to psychological doctrines, but springs from his own innate wisdom.

His monograph should be in the hands of every surgeon who is likely to be called upon to deal with a variety of injury that is distressingly common.

The author is to be congratulated upon this contribution to British surgical literature, and the publishers who have produced a beautiful book deserve our praise also.

The Precentral Cortex. By C. L. Aring, P. Bailey, G. von Bonin, P. C. Bucy, C. Davison, T. C. Erickson, J. F. Fulton, M. Hines, M. A. Kennard, P. M. Levin, W. S. McCulloch, J. O'Leary, W. K. Smith, S. Tower and A. Earl Walker. Edited by P. Bucy. University of Illinois Press. 1944. Pp. 605. Price $4.50.

This considerable monograph by no less than fifteen contributors shows what a vast amount of experimental observation has been devoted to the functions of the precentral cortex, and to what intensive study the minute structure of the

cerebral cortex as a whole has been subjected. It reveals also how many are the aspects from which cerebral structure and functions may be viewed. The mass of available information makes the task of its synthesis and interpretation, and the forming of general conclusions as to the modes of cortical activity all the more difficult, and the student of this monograph will realize that in this matter integration has not kept pace with differentiation.

The aphorism thus brought to mind not only expresses the fundamental principles of evolution of structure and function of the nervous system, but it also aptly indicates what is the truly scientific attitude towards new information: namely, its integration into a coherent body of knowledge and the drawing of general principles from it. Marion Hines in a concluding chapter makes a valiant effort at synthesis, but it is, for the clinical neurologist at least, disappointing to find no adequate presentation of the views of Hughlings Jackson upon the mode of representation of movements in the cerebral cortex. Whatever elements in these views the advance of knowledge may have rendered obsolete, they nevertheless represent the most philosophic and masterly conception yet before us, and to its neglect in the thought of modern experimentalists we owe the persistence of the naïve view of the motor cortex as a more or less fixed mosaic of points in each of which some fragmentary movement or—according to some physiologists—some muscle or portion of a muscle finds a representation. The facts long in our hands have certainly rendered this primitive notion untenable, yet its viability is remarkable and it lingers a disturbing anachronism upon the physiological scene.

In his chapter upon the minute structure of the precentral cortex, von Bonin compares the various current views on cortical fields and stratigraphy, and it is interesting to find at last some critical thought upon the cyto-architectonic studies of the Vogts, and some awareness of the unsatisfactory nature of the view that has hitherto made of the giant cell of Betz a morphological and physiological entity apart from other pyramidal cells in the precentral cortex.

In the purely physiological chapters dealing with the results of cortical excitation and extirpation, the clinical neurologist will be struck by the imperfect ideas as to what constitutes "spasticity" held by experimental physiologists, who, aware only of the grosser forms of hypertonus as seen in experimental animals, tend to regard as flaccid paralyses in which a familiarity with the clinical phenomena of spastic paralysis might have taught them where to find and how to assess hypertonus in its lesser degrees. The fruitful comparison of clinically and experimentally observed phenomena of paralysis and hypertonus requires of both clinician and animal experimentalist a familiarity with one another's material which is too commonly lacking.

One of the most attractive chapters in the monograph is a translation and reprint of Bubnoff and Heidenhain's (1881) paper on "excitatory and inhibitory processes" in the cerebral cortex. Here we find a just balance of observation and ideas and an insight into cortical function that may well serve as an exemplar to modern workers in this field.

Other chapters of special interest are Tower's on the pyramidal tract and Hines on the significance of the precentral cortex. In Bucy's chapter on the results of localized cortical extirpations in man, there purports to be a complete record of published cases, but there is no reference to a recent (1935) and fully documented case of excision of the "leg area" of the motor cortex in a patient of Gordon Holmes reported in this journal by Walshe.

It may be doubted whether the time has yet come for a monograph upon the precentral cortex, when so much observation upon it remains unconfirmed, and

when generalization upon what is established is in so very imperfect a state, but for those anxious to know what has been done up to date the authors provide a rich store of information.

Neuro-Ophthalmology. By D. J. LYLE. Ballière, Tindall and Cox, Ltd., London. 1945.

The author seeks to provide briefly and comprehensively an account of the pathology and clinical aspect of organic nervous affections in which ocular manifestations occur, for the benefit of ophthalmologists.

The general plan of the book, therefore, is that familiar in textbooks of neurology, special stress being laid on ocular disorders seen on the background of nervous disease.

A striking feature of the book is the large number of stereo-photographs of various retinal lesions. There are also numerous photographs of the common pathological lesions of the brain.

An impressive bibliography of over 1,700 papers will prove of great value to those who wish to pursue any aspect of the subject.

The Examination of Reflexes. By R. WARTENBERG. The Year Book Publishers Inc., Chicago. 1945. London, H. K. Lewis. Price $2.50.

The author has been at great pains to go through the clinical literature on the phenomena that pass as "reflexes" in clinical neurology. How vast this is may be seen from the bibliography of over 400 papers which the author provides. It may be attributed as a virtue to neurologists in this country that they have contributed very sparsely to this unwieldy collection of often useless "signs," and as a still greater virtue that they have attached their names to none of them. In respect of both tendon and cutaneous reflexes, it is obvious that their number must be legion if they are sought upon the whole surface, and throughout the skeletal musculature of, the human body, and probable that many remain yet "undiscovered" and waiting for some ambitious clinician to achieve the order of fame that comes from association with an eponymous sign. There are still many areas within the maximal limits of the receptive field of the reflex we speak of as the Babinski plantar response, waiting for the eager to stake their claims on, and we are probably not yet at the end of the variants of this reflex reaction which will come to bear the names of neurologists yet unfledged.

As Foster Kennedy rightly remarks in his foreword, it is time this futile business came to an end. It represents that naïve period of clinical neurology between the earlier age of physiological inspiration in the last quarter of the nineteenth century, and that period of revival which began round about 1914 when the influence of Sherrington's work on clinical thought began to develop.

As was to be expected, Wartenberg has found that many of these reflexes, described and named by different writers, are merely variants of a single reflex, differing in little more than the precise details of their eliciting, or the part of the receptive field from which, in different accounts, they are described as being evoked.

Many more serve no useful purpose whatever. They cumber neurological literature, making it almost unintelligible to the reader who is not a professed neurologist, and, where their employment is current, make neurology the most forbidding of subjects for the student. Almost every digit on hand and foot has its "sign,"

and there is scarcely a bony prominence which on being smitten with a percussion hammer will not yield one. We should be better without the vast majority of them. In the best papers on neurological subjects they rarely figure, and what is needed is not their continued use, as the author of this book seems to desire, under an anatomical nomenclature, but their disappearance from neurological books and papers.

Nevertheless, the author has done a useful work in assembling them within one cover. Many of them may now be consigned to an historical museum as the pathetic relics of one of the less inspiring periods in the history of clinical neurology. There is a relatively small number of reflex phenomena that are useful and significant. Let us decide which these are and, for routine purposes, ruthlessly discard the rest.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By F. R. Ford. Second Edition. 1945. C. C. Thomas, Springfield, Ill. Price $12.50.

Neurologists and pediatricians will give a warm welcome to this second and enlarged edition of Dr. Ford's book. It now runs, alas, to over 1,100 pages, some 190 of which are devoted to methods of examination and to anatomical and physiological considerations, and many more to clinical case records.

The work is plainly one of reference for the specialist, not for student or for general practitioner, and for this role it is excellently adapted, for it is clear, comprehensive, has good bibliographies and a satisfactory index. For this reason one may ask whether the reader of this order will need the anatomical, physiological and methodological chapters, or will be helped by the case records. Their omission would certainly have allowed Dr. Ford's excellent clinical and pathological presentations to stand out more prominently, and would have led to a much-to-be-desired reduction in the bulk, weight and price of the book: surely considerations of some moment to readers in these days of ever more weighty and expensive medical tomes.

Diseases of the Nervous System. Described for Practitioners and Students. By F. M. R. Walshe. Fourth Edition. E. and S. Livingstone, Edinburgh. 1945. Price 15s.

The first edition of this work was reviewed in this Journal in the year of its appearance, 1940. The author has since made such changes and additions as have appeared useful and expedient, but the book still retains its original scope and size.

Child Guidance. By W. M. Burbury, E. M. Balint and B. J. Yapp. Macmillan and Co., Ltd., London. 1945. Price 7s. 6d.

This is an orthodox presentation of the case for and the accepted methods of what has come to be called child guidance. It is the joint production of a psychiatrist, a psychologist and a psychiatric social worker. Within its self-imposed limits it is a readable and useful account, but like all works of the kind it seems to start from the assumption that the child is a disembodied spirit. Of the physical and physiological development of the child, with their constants and their variations, we hear nothing, though consideration will show that we cannot hope to "guide"

children unless and until we take these basic factors into due consideration. Probably of no branch of psychology is the truth of the aphorism "nemo psychologus nisi prius physiologus" more glaringly true, and in no branch of psychology is it more consistently and totally ignored. Here we see "specialism" in its narrowest guise, with all its faults and its excessive concentration upon a partial aspect of its material. Until the child guidance team and clinic includes a physician of wide general experience, broad outlook and a sound knowledge of physical and physiological development, we shall look in vain for anything that can rightly be called child guidance.

Recent Advances in Neurology and Neuropsychiatry. By W. Russell Brain and E. B. Strauss. J. and A. Churchill, Ltd., London. Fifth Edition. 1945. Price 18s.

Hitherto entitled "Recent Advances in Neurology," this valuable summary of recent additions to knowledge now bears the more comprehensive title indicated above, and in its preface the authors define the scope and relationship of neurology and psychiatry as they conceive them. The field of neurology is well covered, and in that of psychiatry there are chapters on convulsant therapy and prefrontal leucotomy. Northfield contributes a chapter on brain injuries. The nature of the book forbids a summary of its contents, but it constitutes a well-chosen, comprehensive and thoughtful survey, and should be in the library of all neurologists and psychiatrists and deserves a wide success.

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CONTENTS

MEERLOO, A. M. A study of treason.

HARRISSON, T. The British soldier : changing attitudes and ideas.

SLATER, P. Scores of different types of neurotics on tests of intelligence.

OBITUARY. Professor G. F. Stout.

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